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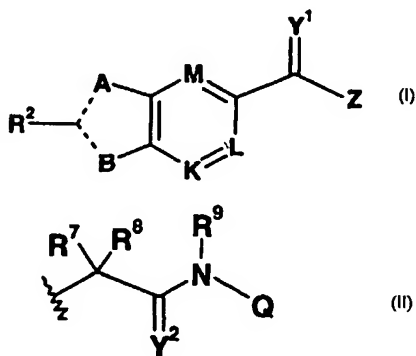
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(54) Title: VIRAL POLYMERASE INHIBITORS



(57) Abstract: An isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I: wherein: A is O, S, NR¹, or CR¹, wherein R¹ is defined herein; represents either a single or a double bond; R² is selected from: H, halogen, R²¹, OR²¹, SR²¹, COOR²¹, SO₂N(R²²)₂, N(R²²)₂, CON(R²²)₂, NR²²C(O)R²² or NR²²C(O)NR²² wherein R²¹ and each R²² is defined herein; B is NR³ or CR³, with the proviso that one of A or B is either CR¹ or CR³, wherein R³ is defined herein; K is N or CR⁴, wherein R⁴ is defined herein; L is N or CR⁵, wherein R⁵ has the same definition as R⁴; M is N or CR⁷, wherein R⁷ has the same definition as R⁴; Y¹ is O or S; Z is N(R^{6a})R⁶ or OR⁶, wherein R^{6a} is H or alkyl or NR⁶¹R⁶² wherein R⁶¹ and R⁶² are defined herein; and R⁶ is H, alkyl, cycloalkyl, alkenyl, Het, alkyl-aryl, alkyl-Het; or R⁶ is wherein R⁷ and R⁸ and Q are as defined herein; Y² is O or S; R⁹ is H, (C₁₋₆ alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het, all of which optionally substituted with R^{9a}; or R⁹ is covalently bonded to either of R⁷ or R⁸ to form a 5- or 6-membered

heterocycle; a salt or a derivative thereof, as an inhibitor of HCV NSSB polymerase.

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VIRAL POLYMERASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The invention relates to inhibitors of RNA dependent RNA polymerases, particularly those viral polymerases within the Flaviviridae family, more particularly to HCV polymerase.

BACKGROUND OF THE INVENTION

About 30,000 new cases of hepatitis C virus (HCV) infection are estimated to occur in the United States each year (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051). HCV is not easily cleared by the hosts' immunological defences; as many as 85% of the people infected with HCV become chronically infected. Many of these persistent infections result in chronic liver disease, including cirrhosis and hepatocellular carcinoma (Hoofnagle, J.H.; 1997; *Hepatology* **26**: 15S-20S*). There are an estimated 170 million HCV carriers world-wide, and HCV-associated end-stage liver disease is now the leading cause of liver transplantation. In the United States alone, hepatitis C is responsible for 8,000 to 10,000 deaths annually. Without effective intervention, the number is expected to triple in the next 10 to 20 years. There is no vaccine to prevent HCV infection.

Prolonged treatment of chronically infected patients with interferon or interferon and ribavirin is the only currently approved therapy, but it achieves a sustained response in fewer than 50% of cases (Lindsay, K.L.; 1997; *Hepatology* **26**: 71S-77S*, and Reichard, O.; Schvarcz, R.; Weiland, O.; 1997 *Hepatology* **26**: 108S-111S*).

HCV belongs to the family *Flaviviridae*, genus *hepacivirus*, which comprises three genera of small enveloped positive-strand RNA viruses (Rice, C.M.; 1996; "Flaviviridae: the viruses and their replication"; pp. 931-960 in *Fields Virology*, Fields, B.N.; Knipe, D.M.; Howley, P.M. (eds.); Lippincott-Raven Publishers, Philadelphia Pa. *). The 9.6 kb genome of HCV consists of a long open reading frame (ORF) flanked by 5' and 3' non-translated regions (NTR's). The HCV 5' NTR is 341 nucleotides in length and functions as an internal ribosome entry site for cap-independent translation initiation (Lemon, S.H.; Honda, M.; 1997; *Semin. Virol.* **8**: 274-288). The HCV polyprotein is cleaved co- and post-translationally into at least 10 individual polypeptides (Reed, K.E.; Rice, C.M.; 1999; *Curr. Top. Microbiol. Immunol.* **242**: 55-84*). The structural proteins result from signal peptidases in the N-

terminal portion of the polyprotein. Two viral proteases mediate downstream cleavages to produce non-structural (NS) proteins that function as components of the HCV RNA replicase. The NS2-3 protease spans the C-terminal half of the NS2 and the N-terminal one-third of NS3 and catalyses *cis* cleavage of the NS2/3 site.

5 The same portion of NS3 also encodes the catalytic domain of the NS3-4A serine protease that cleaves at four downstream sites. The C-terminal two-thirds of NS3 is highly conserved amongst HCV isolates, with RNA-binding, RNA-stimulated NTPase, and RNA unwinding activities. Although NS4B and the NS5A phosphoprotein are also likely components of the replicase, their specific roles are

10 unknown. The C-terminal polyprotein cleavage product, NS5B, is the elongation subunit of the HCV replicase possessing RNA-dependent RNA polymerase (RdRp) activity (Behrens, S.E.; Tomei, L.; DeFrancesco, R.; 1996; *EMBO J.* **15**: 12-22*; and Lohmann, V.; Körner, F.; Herian, U.; Bartenschlager, R.; 1997; *J. Virol.* **71**: 8416-8428*). It has been recently demonstrated that mutations destroying NS5B activity

15 abolish infectivity of RNA in a chimp model (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051*).

The development of new and specific anti-HCV treatments is a high priority, and virus-specific functions essential for replication are the most attractive targets for

20 drug development. The absence of RNA dependent RNA polymerases in mammals, and the fact that this enzyme appears to be essential to viral replication, would suggest that the NS5B polymerase is an ideal target for anti-HCV therapeutics.

WO 00/06529 reports inhibitors of NS5B which are α , γ -diketoacids.

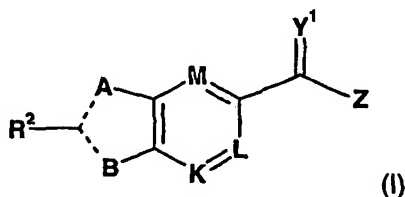
WO 00/13708, WO 00/10573, WO 00/18231, and WO 01/47883 report inhibitors of

25 NS5B proposed for treatment of HCV.

SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a novel series of compounds having improved inhibitory activity against HCV polymerase.

In a first aspect of the invention, there is provided an isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I:



wherein:

- 5 **A** is O, S, NR¹, or CR¹, wherein R¹ is selected from the group consisting of: H, (C₁₋₆)alkyl optionally substituted with:
- halogen, OR¹¹, SR¹¹ or N(R¹²)₂, wherein R¹¹ and each R¹² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het, said aryl or Het optionally substituted with R¹⁰; or
- 10 both R¹² are covalently bonded together and to the nitrogen to which they are both attached to form a 5, 6 or 7-membered saturated heterocycle;

---- represents either a single or a double bond;

- 15 R² is selected from: halogen, R²¹, OR²¹, SR²¹, COOR²¹, SO₂N(R²²)₂, N(R²²)₂, CON(R²²)₂, NR²²C(O)R²² or NR²²C(O)NR²² wherein R²¹ and each R²² is independently H, (C₁₋₆)alkyl, haloalkyl, (C₂₋₆)alkenyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkynyl, (C₅₋₇)cycloalkenyl, 6 or 10-membered aryl or Het, said R²¹ and R²² being optionally substituted with R²⁰;
- 20 or both R²² are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

- B** is NR³ or CR³, with the proviso that one of **A** or **B** is either CR¹ or CR³, wherein R³ is selected from (C₁₋₆)alkyl, haloalkyl, (C₃₋₇)cycloalkyl, (C₅₋₇)cycloalkenyl, (C₆₋₁₀)bicycloalkyl, (C₆₋₁₀)bicycloalkenyl, 6- or 10-membered aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het,
- 25

said alkyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, Het, alkyl-aryl and alkyl-Het being optionally substituted with from 1 to 4 substituents selected from: halogen, or

- 30 a) (C₁₋₆)alkyl optionally substituted with:
- OR³¹ or SR³¹ wherein R³¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl,

(C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-**Het**; or

- N(R³²)₂ wherein each R³² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-**Het**; or both R³² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) OR³³ wherein R³³ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-**Het**;

c) SR³⁴ wherein R³⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-**Het**;

and
d) N(R³⁵)₂ wherein each R³⁵ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-**Het**; or both R³⁵ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

K is N or CR⁴, wherein R⁴ is H, halogen, (C₁₋₆)alkyl, haloalkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or R⁴ is OR⁴¹ or SR⁴¹, COR⁴¹ or NR⁴¹COR⁴¹ wherein each R⁴¹ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or R⁴ is NR⁴²R⁴³ wherein R⁴² and R⁴³ are each independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, or both R⁴² and R⁴³ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

L is N or CR⁵, wherein R⁵ has the same definition as R⁴ defined above;

M is N or CR⁷, wherein R⁷ has the same definition as R⁴ defined above;

Y¹ is O or S;

Z is OR⁶ wherein R⁶ is C₁₋₆alkyl substituted with:

- 1 to 4 substituents selected from: OPO₃H, NO₂, cyano, azido, C(=NH)NH₂,

$C(=NH)NH(C_{1-6})alkyl$ or $C(=NH)NHCO(C_{1-6})alkyl$; or

- 1 to 4 substituents selected from:

- a) $(C_{1-6})alkyl$ or haloalkyl, $(C_{3-7})cycloalkyl$, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, $(C_{2-6})alkenyl$, $(C_{2-6})alkynyl$, $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, all of which optionally substituted with R^{150} ;
- b) OR^{104} wherein R^{104} is $(C_{1-6})alkyl$ substituted with R^{150} , $(C_{3-7})cycloalkyl$, or $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het, said cycloalkyl, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het being optionally substituted with R^{150} ;
- c) $OCOR^{105}$ wherein R^{105} is $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$, $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het, said alkyl, cycloalkyl, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het being optionally substituted with R^{150} ;
- d) SR^{108} , SO_3H , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$ or $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het or heterocycle being optionally substituted with R^{150} ;
- e) $NR^{111}R^{112}$ wherein R^{111} is H, $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$ or $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het, and R^{112} is H, CN, $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$ or $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, aryl, Het, $(C_{1-6})alkyl$ aryl, $(C_{1-6})alkyl$ Het, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$, or $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, $(C_{1-6})alkyl$ aryl, $(C_{1-6})alkyl$ Het, or heterocycle being optionally substituted with R^{150} ;
- f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$, $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het, said $(C_{1-6})alkyl$, $(C_{3-7})cycloalkyl$, $(C_{1-6})alkyl-(C_{3-7})cycloalkyl$, aryl, Het, $(C_{1-6})alkyl$ aryl or $(C_{1-6})alkyl$ Het being optionally substituted with R^{150} ;

- g) $\text{NR}^{118}\text{CONR}^{119}\text{R}^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
 5 or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
 said alkyl, cycloalkyl, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ or heterocycle being optionally substituted with R^{150} ;
- h) $\text{NR}^{121}\text{COCOR}^{122}$ wherein R^{121} and R^{122} is each H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, a 6- or 10-membered aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ being optionally substituted with R^{150} ;
 10 or R^{122} is OR^{123} or $\text{N}(\text{R}^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(\text{C}_{1-6}\text{alkyl})$, $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or R^{124} is OH or $\text{O}(\text{C}_{1-6}\text{alkyl})$ or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ and heterocycle being optionally substituted with R^{150} ;
- i) COR^{127} wherein R^{127} is H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$ or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, said alkyl, cycloalkyl, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ being optionally substituted with R^{150} ;
- 15 j) COOR^{128} wherein R^{128} is $(\text{C}_{1-6})\text{alkyl}$ substituted with R^{150} , $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, said $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ and $(\text{C}_{1-6}\text{alkyl})\text{Het}$ being optionally substituted with R^{150} ;
- 20 k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$, $(\text{C}_{1-6}\text{alkyl})\text{Het}$ and heterocycle being optionally substituted with R^{150} ;
- 25 l) aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, all of which being optionally substituted with R^{150} ;
- 30 wherein R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO₂, cyano, azido or

- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁶⁰;

c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁵⁰;

d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or heterocycle being optionally substituted with R¹⁶⁰;

e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, and R¹¹² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;

f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted

with R^{160} ;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R^{160} ;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C₁₋₆)alkyl optionally substituted with R^{160} , and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R^{124} is OH or O(C₁₋₆alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R^{160} ;

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R^{160} ; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R^{160} ;

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, $COOR^{161}$, SO_3H , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$, or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to

which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or Z is OR⁶ wherein R⁶ is (C₁₋₆alkyl)aryl substituted with:

- 5 - 1 to 4 substituents selected from: OPO₃H, azido, C(=NH)NH₂,
C(=NH)NH(C₁₋₆)alkyl or C(=NH)NHCO(C₁₋₆)alkyl; or
- 1 to 4 substituents selected from:
- 10 a) (C₁₋₆)alkyl substituted with R^{150a}, haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇
spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋
8)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl,
alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R¹⁵⁰,
wherein R^{150a} is the same as R¹⁵⁰ but is not COOR^{150b}, N(R^{150b})₂,
NR^{150b}C(O)R^{150b}, OR^{150b}, SR^{150b}, SO₂R^{150b}, SO₂N(R^{150b})₂, wherein R^{150b} is H
or unsubstituted C₁₋₆alkyl;
- 15 b) OR¹⁰⁴ wherein R¹⁰⁴ is (C₁₋₆alkyl) substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or
(C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said
cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally
substituted with R¹⁵⁰;
- 20 c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋
7)cycloalkyl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl,
Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- 25 d) SR^{108a}, SO₂N(R^{108a})₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is
independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl,
Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R¹⁰⁸ are covalently bonded
together and to the nitrogen to which they are attached to form a 5, 6 or 7-
membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋
6alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with
R¹⁵⁰, wherein R^{108a} is the same as R¹⁰⁸ but is not H or unsubstituted C₁₋₆alkyl;
- 30 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋
7)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R¹¹² is H, CN, (C₁₋
6alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl,
(C₁₋₆alkyl)Het, provided that when R¹¹¹ is H or unsubstituted alkyl, R¹¹² is not
H or unsubstituted alkyl,
or R¹¹² is also COOR¹¹⁵ or SO₂R^{115a} wherein R¹¹⁵ is H, (C₁₋₆)alkyl, (C₃₋

- 7)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R^{115a} is the same as R¹¹⁵ but is not H or unsubstituted alkyl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 5 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 10 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 15 h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;
- 20 i) COR¹²⁷ wherein R¹²⁷ is (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 25 j) COOR¹²⁸ wherein R¹²⁸ is (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 30

₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, provided that when R¹²⁹ is H or unsubstituted alkyl, R¹³⁰ is not H or unsubstituted alkyl,

or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰; and wherein R¹⁵⁰ is

- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido;

- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋

- ₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and **R**¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein **R**¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both **R**¹¹¹ and **R**¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with **R**¹⁶⁰;
- f) NR**¹¹⁶**COR**¹¹⁷ wherein **R**¹¹⁶ and **R**¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁶⁰;
- g) NR**¹¹⁸**CONR**¹¹⁹**R**¹²⁰, wherein **R**¹¹⁸, **R**¹¹⁹ and **R**¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or **R**¹¹⁸ and **R**¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with **R**¹⁶⁰;
- h) NR**¹²¹**COCOR**¹²² wherein **R**¹²¹ is H, (C₁₋₆)alkyl optionally substituted with **R**¹⁶⁰; and **R**¹²² is OR¹²³ or N(**R**¹²⁴)₂ wherein **R**¹²³ and each **R**¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or **R**¹²⁴ is OH or O(C₁₋₆alkyl) or both **R**¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with **R**¹⁶⁰;
- i) tetrazole, COOR**¹²⁸ wherein **R**¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁶⁰; and

k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)**Het** and heterocycle being optionally substituted with R^{160} ;

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, COOR^{161} , SO_3H , $\text{SO}_2\text{R}^{161}$, OR^{161} , $\text{N}(\text{R}^{162})_2$, $\text{SO}_2\text{N}(\text{R}^{162})_2$, $\text{NR}^{162}\text{COR}^{162}$ or $\text{CON}(\text{R}^{162})_2$, wherein R^{161} and R^{162} are as defined above;

or **Z** is OR^6 wherein R^6 is, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-**Het**, wherein said cycloalkyl, alkenyl, aryl, **Het** or alkyl-**Het**, is optionally substituted with R^{60} ;

or **Z** is $\text{N}(\text{R}^{6a})\text{R}^6$, wherein R^{6a} is H or (C_{1-6}) alkyl and

R^6 is (C_{1-6}) alkyl optionally substituted with:

- 1 to 4 substituents selected from: OPO_3H , NO_2 , cyano, azido, $\text{C}(=\text{NH})\text{NH}_2$,

$\text{C}(=\text{NH})\text{NH}(\text{C}_{1-6})$ alkyl or $\text{C}(=\text{NH})\text{NHCO}(\text{C}_{1-6})$ alkyl; or

- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl substituted with R^{150a} , haloalkyl substituted with R^{150} , (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} , wherein R^{150a} is the same as R^{150} but is not halogen,

OH , $\text{O}(\text{C}_{1-6})$ alkyl, COOH , $\text{COO}(\text{C}_{1-6})$ alkyl, NH_2 , $\text{NH}(\text{C}_{1-6})$ alkyl and $\text{N}(\text{C}_{1-6})$ alkyl) $_2$;

b) OR^{104} wherein R^{104} is (C_{1-6}) alkyl substituted with R^{150} , (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;

c) OCOR^{105} wherein R^{105} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;

d) SR^{108} , SO_3H , $\text{SO}_2\text{N}(\text{R}^{108})_2$ or $\text{SO}_2\text{N}(\text{R}^{108})\text{C}(\text{O})\text{R}^{108}$ wherein each R^{108} is

- independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or heterocycle being optionally substituted with R¹⁵⁰;
- 5 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, provided that when R¹¹¹ is H or unsubstituted alkyl, R¹¹² is not H or unsubstituted alkyl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or heterocycle being optionally substituted with R¹⁵⁰;
- 10 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁵⁰;
- 15 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or heterocycle being optionally substituted with R¹⁵⁰;
- 20 h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁵⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋
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₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

5 **i) COR¹²⁷** wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

j) COOR¹²⁸ wherein R¹²⁸ is (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

10 **k) CONR¹²⁹R¹³⁰** wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

15 **l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het**, all of which being optionally substituted with R¹⁵⁰, wherein R¹⁵⁰ is selected from:

20 - 1 to 3 substituents selected from: halogen, NO₂, cyano, azido or
- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

25 **b) OR¹⁰⁴** wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

30 **c) OCOR¹⁰⁵** wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋

γ)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R^{160} ;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R^{112} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R^{115} is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R^{160} ;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R^{160} ;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R^{160} ;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C₁₋₆)alkyl optionally substituted with R^{160} , and R^{122} is OR¹²³ or N(R¹²⁴)₂ wherein R^{123} and each R^{124} is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R^{124} is OH or O(C₁₋₆alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle

being optionally substituted with R^{160} ;

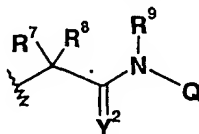
j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-**Het**, said (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl-aryl and (C_{1-6}) alkyl-**Het** being optionally substituted with R^{160} ;

and
k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het** and heterocycle being optionally substituted with R^{160} ;

wherein R^{160} is defined as 1 or 2 substituents selected from:
tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, SO_3H , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above;

or Z is $N(R^{6a})R^6$ wherein R^{6a} is as defined above and R^6 is (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, wherein said alkyl, cycloalkyl, alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with R^{60} ;

or Z is OR^6 or $N(R^{6a})R^6$ wherein R^{6a} is as defined above and R^6 is:



wherein R^7 and R^8 are each independently H, (C_{1-6}) alkyl, haloalkyl, (C_{3-7}) cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het** are optionally substituted with R^{70} ;

or

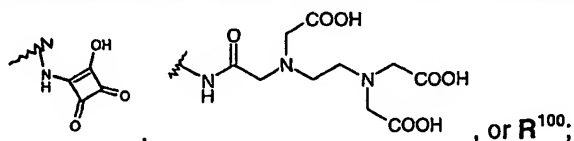
R^7 and R^8 are covalently bonded together to form second (C_{3-7}) cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when Z is $N(R^{6a})R^6$, either of R^7 or R^8 is covalently bonded to R^{6a} to form a

nitrogen-containing 5- or 6-membered heterocycle;

Y^2 is O or S;

- 5 R^9 is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-**Het**, all of which optionally substituted with R^{80} ; or
 R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle;

- Q is a 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, (C_{1-6}) alkyl-
 10 CONH-aryl or (C_{1-6}) alkyl-CONH-**Het**, all of which being optionally substituted with:



or a salt or a derivative thereof;

- wherein **Het** is defined as 5- or 6-membered heterocycle having 1 to 4 heteroatoms
 15 selected from O, N, and S, or a 9- or 10-membered heterobicyclic having 1 to 5
 heteroatoms selected from O, N and S; and

R^{10} , R^{20} , R^{60} , R^{70} , R^{90} and R^{100} is each defined as:

- 1 to 4 substituents selected from: halogen, OPO_3H , NO_2 , cyano, azido,
 20 $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$ alkyl or $C(=NH)NHCO(C_{1-6})$ alkyl; or
 - 1 to 4 substituents selected from:
 a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally
 containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-8}) alkynyl, (C_{1-6}) alkyl- (C_{3-7})
 cycloalkyl, all of which optionally substituted with R^{150} ;
 25 b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7})
 cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-**Het**, said alkyl, cycloalkyl,
 aryl, **Het**, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-**Het** being optionally substituted with
 R^{150} ;
 c) $OCOR^{105}$ wherein R^{105} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7})
 cycloalkyl, **Het**, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-**Het**, said alkyl, cycloalkyl, aryl,
 30 **Het**, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-**Het** being optionally substituted with R^{150} ;
 d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

- independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 5 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 10 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 15 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 20 **h)** NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are
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covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰; and

wherein R¹⁵⁰ is defined as:

- 1 to 3 substituents selected from: halogen, OPO₃H, NO₂, cyano, azido, C(=NH)NH₂, C(=NH)NH(C₁₋₆)alkyl or C(=NH)NHCO(C₁₋₆)alkyl; or

- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

- d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R^{160} ;
- e) $NR^{111}R^{112}$ wherein R^{111} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R^{112} is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R^{115} is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R^{160} ;
- f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R^{160} ;
- g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R^{160} ;
- h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl,

aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰, or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁶⁰;

i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰; and

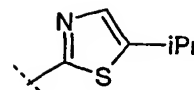
k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁶⁰;

wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SR¹⁶¹, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl; or both R¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,

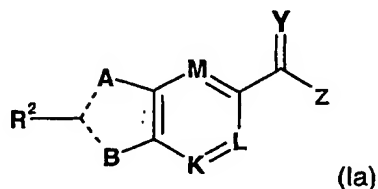
or a salt thereof,

with the proviso that, when A is CH, R² is phenyl or N-butyl, B is NR³, R³ is Me, K is

CH, L is CH, M is CH, Y¹ is O, and Z is NHR⁶, then R⁶ is not



Alternatively, in a first aspect of the invention, there is provided a compound represented by Formula Ia:



5 wherein:

A is O, S, NR¹, or CR¹;

B is NR³ or CR³;

R¹ is selected from the group consisting of: H, (C₁₋₆)alkyl, benzyl, (C₁₋₆ alkyl)-(C₆₋₁₀aryl), (C₁₋₆ alkyl)-5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, and 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

15 wherein said benzyl and said heteroatom are optionally substituted with from 1 to 4 substituents selected from the group consisting of: COOH, COO(C₁₋₆ alkyl), halogen, and (C₁₋₆ alkyl);

R² is selected from the group consisting of: H, halogen, (C₁₋₆)alkyl; (C₃₋₇)cycloalkyl, phenyl, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, pyridine-N-oxide, and 9- or 10-membered heterobicyclic having 1 to 4 heteroatoms selected from O, N and S,

said phenyl, heterocycle and heterobicyclic being optionally substituted with from 1 to 4 substituents selected from the group consisting of: halogen, C(halogen)₃, (C₁₋₆)alkyl, OH, O(C₁₋₆ alkyl), NH₂, and N(C₁₋₆ alkyl)₂;

25 R³ is selected from the group consisting of: 5-, 6- or 7-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, norbornane, (C₃₋₇)cycloalkyl and (C₃₋₇)cycloalkyl-(C₁₋₆ alkyl);

M is N, CR⁴, or COR⁵, wherein R⁴ is selected from the group consisting of: H,

halogen, and (C₁₋₆ alkyl); and R⁵ is selected from the group consisting of: H and (C₁₋₆ alkyl);

K and L is N or CH;

5

----- represents either a single or a double bond;

Y is O or S;

Z is OR⁶ or NR⁶R^{6a}

10

R⁶ is selected from the group consisting of: H, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₆)alkyl, (C₆₋₁₀)aryl, (C₆₋₁₀)aryl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₃₋₆)cycloalkyl(C₂₋₆)alkenyl, (C₆₋₁₀)aryl(C₂₋₆)alkenyl, N{(C₁₋₆) alkyl}₂, NHCOO(C₁₋₆)alkyl(C₆₋₁₀)aryl, NHCO(C₆₋₁₀)aryl, (C₁₋₆)alkyl-5- or 6-atom heterocycle, having 1 to 4
15 heteroatoms selected from O, N and S, and 9- or 10-atom heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

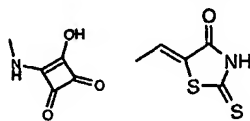
wherein said alkyl, cycloalkyl, aryl, alkenyl, heterocycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C₁₋₆)alkyl, (C₁₋₆)alkyl, (C₁₋₆)alkyl-hydroxy, phenyl, benzyloxy, halogen, (C₂₋₄)alkenyl, (C₂₋₄)alkenyl-(C₁₋₆)alkyl-COOH, 5- or 6-membered heterocycle
20 having 1 to 4 heteroatoms selected from O, N and S,

wherein said alkyl, cycloalkyl, aryl, alkenyl and heterocycle being optionally substituted with from 1 to 4 substituents selected from: (C₁₋₆ alkyl), CF₃, OH, COOH, NHC(C₁₋₆alkyl)₂, NHCO(C₁₋₆ alkyl), NH₂, NH(C₁₋₆ alkyl), and
25 N(C₁₋₆ alkyl)₂;

9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S, said heterobicycle being optionally substituted with from 1 to 4
30 substituents selected from:

halogen, OPO₃H, sulfonamido, SO₃H, SO₂CH₃, -CONH₂, -COCH₃, (C₁₋₃)alkyl, (C₂₋₄alkenyl)COOH, tetrazolyl, COOH, -CONH₂, triazolyl, OH, NO₂, NH₂, -O(C₁₋₆ alkyl)COOH, hydantoin, benzoyleneurea, (C₁₋₄)alkoxy, cyano, azido, -O-(C₁₋₆)alkyl COOH, -O-(C₁₋₆)alkyl COO-(C₁₋₆)alkyl, NHCO(C₁₋
35

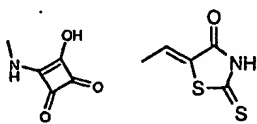
₆ alkyl), -NHCOCOOH, -NHCOCONHOH, -NHCOCONH₂,
 -NHCOCONHCH₃, -NHCO(C₁₋₆)alkyl-COOH,
 -NHCOCONH(C₁₋₆)alkyl-COOH, -NHCO(C₃₋₇)cycloalkyl-
 COOH, -NHCONH(C₆₋₁₀)aryl-COOH, -NHCONH(C₆₋₁₀)aryl-
 COO(C₁₋₆)alkyl, -NHCONH(C₁₋₆)alkyl-COOH, -NHCONH(C₁₋₆)
 alkyl-COO(C₁₋₆)alkyl, -NHCONH(C₁₋₆)alkyl-(C₂₋₆)alkenyl-
 COOH, -NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-O(C₁₋₆)alkyl COOH, -NH(C₁₋₆)
 alkyl-(C₆₋₁₀)aryl-COOH, -NHCH₂COOH, -NHCONH₂,
 -NHCO(C₁₋₆)hydroxyalkyl COOH, -OCO(C₁₋₆)hydroxyalkyl
 COOH, (C₃₋₆)cycloalkyl COOH,



, -NHCN, -NHCHO, -NHSO₂CH₃, and
 -NHSO₂CF₃;

6- or 10-membered aryl being optionally substituted with from 1 to 4
 substituents selected from:

halogen, OPO₃H, sulfonamido, SO₃H, SO₂CH₃, -CONH₂,
 -COCH₃, (C₁₋₃)alkyl, (C₂₋₄alkenyl)COOH, tetrazolyl, COOH,
 -CONH₂, triazolyl, OH, NO₂, NH₂, -O(C₁₋₆ alkyl)COOH,
 hydantoin, benzoyleneurea, (C₁₋₄)alkoxy, cyano, azido,
 -O-(C₁₋₆)alkyl COOH, -O-(C₁₋₆)alkyl COO-(C₁₋₆)alkyl, NHCO(C₁₋₆
 alkyl), -NHCOCOOH, -NHCOCONHOH, -NHCOCONH₂,
 -NHCOCONHCH₃, -NHCO(C₁₋₆)alkyl-COOH,
 -NHCOCONH(C₁₋₆)alkyl-COOH, -NHCO(C₃₋₇)cycloalkyl-
 COOH, -NHCONH(C₆₋₁₀)aryl-COOH, -NHCONH(C₆₋₁₀)aryl-
 COO(C₁₋₆)alkyl, -NHCONH(C₁₋₆)alkyl-COOH, -NHCONH(C₁₋₆)
 alkyl-COO(C₁₋₆)alkyl, -NHCONH(C₁₋₆)alkyl-(C₂₋₆)alkenyl-
 COOH, -NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-O(C₁₋₆)alkyl COOH, -NH(C₁₋₆)
 alkyl-(C₆₋₁₀)aryl-COOH, -NHCH₂COOH, -NHCONH₂,
 -NHCO(C₁₋₆)hydroxyalkyl COOH, -OCO(C₁₋₆)hydroxyalkyl
 COOH, (C₃₋₆)cycloalkyl COOH,

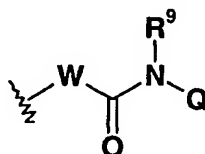


, -NHCN, -NHCHO, -NHSO₂CH₃, and

-NHSO₂CF₃;
 coumarin, (C₁₋₆)alkyl-amino, NH(C₁₋₆ alkyl), C(halogen)₃,
 -NH(C₂₋₄)acyl, -NH(C₆₋₁₀)aroyl, -O(C₁₋₆alkyl)-Het;

- 5 **R^{6a}** is H or (C₁₋₆ alkyl) covalently bonded to either **R⁷** or **R⁸** to form pyrrolidine;

or **Z** is



wherein

- 10 **W** is **CR⁷R⁸** wherein **R⁷** and **R⁸** are each independently H, (C₁₋₆ alkyl), (C₃₋₇ cycloalkyl), (C₁₋₆ alkyl)phenyl, (C₁₋₆ alkyl)-(C₃₋₇ cycloalkyl), (C₃₋₇ cycloalkyl)-(C₁₋₆ alkyl), (C₃₋₇ cycloalkyl)-(C₂₋₄ alkenyl), (C₁₋₆ alkyl)-OH, phenyl, CH₂biphenyl, 5- or 6-membered heterocycle having from 1 to 4 heteroatoms selected from O, N, and S,
 15 S, (C₁₋₆ alkyl)-5- or 6-membered heterocycle having from 1 to 4 heteroatoms selected from O, N, and S, or (C₁₋₆ alkyl)-9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S,
 or **R⁷** and **R⁸** are covalently bonded together to form (C₃₋₇ cycloalkyl), 4-, 5- or 6-membered heterocycle having from 1 to 4 heteroatoms selected from O, N, and S;
 20 or one of **R⁷** or **R⁸** is covalently bonded to **R⁹** to form a pyrrolidine;
 wherein said alkyl, cycloalkyl, heterocycle, heterobicycle, phenyl are optionally substituted with from 1 to 4 substituents selected from the group consisting of: OH, COOH, (C₁₋₆ alkyl), (C₂₋₄ alkenyl), CONH₂, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOCOOH, NHCOCOCON(C₁₋₆ alkyl)₂, NHCOCOCONH(C₁₋₆ alkyl), SH, S(C₁₋₆ alkyl), NHC(=NH)NH₂, halogen, and COO(C₁₋₆alkyl);
 25

R⁹ is H or (C₁₋₆ alkyl); and

- Q** is selected from the group consisting of: (C₁₋₃alkyl)CONHaryl, 6-, 9-, or
 30 10-membered aryl, biphenyl, 5- or 6-atom heterocycle having 1 to 4 heteroatoms selected from O, N and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

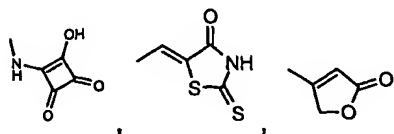
wherein said aryl, biphenyl, heterocycle and heterobicyclic are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C₁₋₆)alkyl, (C₁₋₆)alkyl, (C₁₋₆)alkylCOOH, (C₁₋₆ alkyl)(C₂₋₄ alkenyl), (C₁₋₆)alkyl-hydroxy, phenyl, benzyloxy, halogen, (C₂₋₄)alkenyl, (C₂₋₄)alkenyl-(C₁₋₆)alkyl-COOH, 5- or 6-membered second heterocycle having 1 to 4 heteroatoms selected from O, N and S, NH-5- or 6- membered second heterocycle having 1 to 4 heteroatoms selected from O, N, and S,

wherein said second heterocycle and phenyl being optionally substituted with from 1 to 4 substituents selected from: (C₁₋₆ alkyl), CF₃, OH, (C₁₋₆alkyl) COOH, O(C₁₋₆alkyl)COOH, (C₁₋₆alkyl) COO(C₁₋₆alkyl), CH₂phenyl, COO(C₁₋₆ alkyl), (C₁₋₆alkyl)O(C₁₋₆alkyl), COOH, NCH(C₁₋₆alkyl)₂, NCO(C₁₋₆ alkyl), NH₂, NH(C₁₋₆ alkyl), halogen, and N(C₁₋₆ alkyl)₂;

halogen, OPO₃H, benzyl, sulfonamido, SH, SOCH₃, SO₃H, SO₂CH₃, S(C₁₋₆ alkyl)COOH, -CONH₂, -COCH₃, (C₁₋₃)alkyl, (C₂₋₄alkenyl)COOH

wherein said alkenyl is optionally substituted with from 1 to 2 (C₁₋₆ alkyl) substituents,

(C₂₋₄alkenyl)COO(C₁₋₆alkyl), tetrazolyl, COOH, triazolyl, OH, NO₂, NH₂, , - O(C₁₋₆ alkyl)COOH, hydantoin, benzoyleneurea, (C₁₋₄)alkoxy, (C₁₋₄)alkoxy(C₁₋₆ alkyl)COOH, cyano, azido, -O-(C₁₋₆)alkyl COOH, -O-(C₁₋₆)alkyl COO-(C₁₋₆)alkyl, -NHCOCOOH, -NHCOCONHOH, -NHCOCONH₂, -NHCOCONHCH₃, -NHCO(C₁₋₆)alkyl-COOH, -NHCOCONH(C₁₋₆)alkyl-COOH, -NHCO(C₃₋₇)cycloalkyl-COOH, -NHCONH(C₆₋₁₀)aryl-COOH, - NHCONH(C₆₋₁₀)aryl-COO(C₁₋₆)alkyl, - NHCONH(C₁₋₆)alkyl-COOH, - NHCONH(C₁₋₆)alkyl-COO(C₁₋₆)alkyl, - NHCONH(C₁₋₆)alkyl-(C₂₋₆)alkenyl-COOH, - NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-O(C₁₋₆)alkyl COOH, - NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-COOH, -NHCH₂COOH, -NHCONH₂, -NHCO(C₁₋₆)hydroxyalkyl COOH, -OCO(C₁₋₆)hydroxyalkyl COOH, (C₃₋₈)cycloalkyl COOH,



, -NHCN, -NHCHO, -NHSO₂CH₃, -NHSO₂CF₃, coumarin, (C₁₋₆)alkyl-amino, NH(C₁₋₆alkyl)₂, C(halogen)₃, -NH(C₂₋₄)acyl, -NH(C₆₋₁₀)aroyl, -CONH(C₁₋₆alkyl), -CO(C₁₋₆)alkyl-COOH, -CONH(C₁₋₆)alkyl-COOH, -CO-NH-alanyl, -CONH(C₂₋₄)alkylIN(C₁₋₆alkyl)₂, -CONH(C₂₋₄) alkyl-Het,

-CONH(C₂₋₄) alkyl-(COOH)-Het, -CONH(C₁₋₂ alkyl) (OH)(C₁₋₂ alkyl)OH,
-CONH(C₁₋₆) alkyl-COOH, -CONH(C₆₋₁₀ aryl), -CONH-Het,
-CONH(C₆₋₁₀) aryl-COOH, -CONH(C₆₋₁₀) aryl-COO(C₁₋₆) alkyl,
-CONH(C₁₋₆) alkyl-COO(C₁₋₆) alkyl, -CONH(C₆₋₁₀) aryl-(C₁₋₆)alkyl-COOH, and
5 -CONH(C₆₋₁₀) aryl-(C₂₋₆)alkenyl-COOH,
or a salt thereof.

In a third aspect of the invention, there is provided a compound of the formula I, or a
pharmaceutically acceptable salt thereof, as an inhibitor of RNA dependent RNA
10 polymerase activity of the enzyme NS5B, encoded by HCV.

In a fourth aspect of the invention, there is provided a compound of the formula I, or
a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

15 In a fifth aspect of the invention, there is provided a method of treating or preventing
HCV infection in a mammal, comprising administering to the mammal an effective
amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In a sixth aspect of the invention, there is provided a pharmaceutical composition for
20 the treatment or prevention of HCV infection, comprising an effective amount of a
compound of formula I, or a pharmaceutically acceptable salt thereof, and a
pharmaceutically acceptable carrier.

According to a specific embodiment, the pharmaceutical compositions of this
25 invention comprise an additional immunomodulatory agent. Examples of additional
immunomodulatory agents include but are not limited to, α -, β -, δ - γ -, and ω -
interferons.

According to an alternate embodiment, the pharmaceutical compositions of this
30 invention may additionally comprise an antiviral agent. Examples of antiviral agents
include, ribavirin and amantadine.

According to another alternate embodiment, the pharmaceutical compositions of this
invention may additionally comprise other inhibitors of HCV protease.

According to yet another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an inhibitor of other targets in the HCV life cycle, such as helicase, polymerase, metalloprotease or IRES.

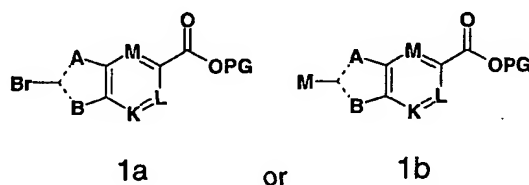
- 5 In a seventh aspect of the invention, there is provided a use of a compound of formula I, for the manufacture of a medicament for the treatment of HCV infection.

In a eighth aspect of the invention, there is provided a use of a compound of formula I, to prevent HCV infection.

10

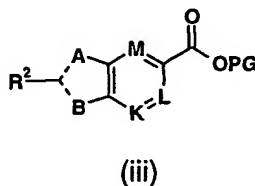
In an ninth aspect of the invention, there is provided a use of a compound of formula I, as an HCV polymerase inhibitor.

- 15 In a tenth aspect of the invention, there is provided an intermediate of formula (1a) or (1b):



wherein **A**, **B**, **K**, **L**, and **M** are as described herein and **PG** is H or a carboxy protecting group.

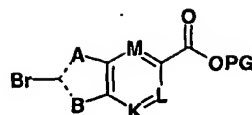
- 20 In a eleventh aspect of the invention, there is provided a process for producing compounds of formula (iii),



wherein **A**, **R²**, **B**, **K**, **L**, **M**, and **PG** are as described herein, comprising:

- 25 a) coupling, in the presence of a metal catalyst (such as, for example, Pd, Ni, Ru, Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1a)

30

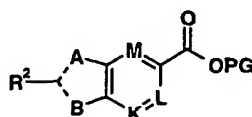


1a

with R^2-X , wherein R^1 , R^3 , K , L , M and PG are as described herein and X is (but not limited to): $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, metal halide, $B(OH)_2$, and $B(O(C_{1-6}alkyl)_2)$ to produce compounds of formula (iii).

5

In an alternative to the eleventh aspect of the invention, there is provided a process for producing compounds of formula (iii),

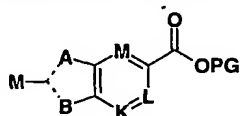


(iii)

wherein A , R^2 , B , K , L , M , and PG are as described herein,

10 comprising:

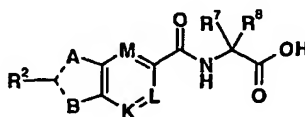
b) coupling, in the presence of a metal catalyst (such as, for example, Pd , Ni , Ru , Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1b)



1b

15 with R^2-X' , wherein X' is halide, $OSO_2(C_{1-6}alkyl)$, OSO_2Ar , OSO_2CF_3 and the like, and M is a metal such as Li , $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, $B(OH)_2$, $B(OC_{1-6}alkyl)_2$, metal halide, to produce compounds of formula (iii).

20 In an thirteenth aspect of the invention, there is provided an intermediate compound represented by formula 1c:



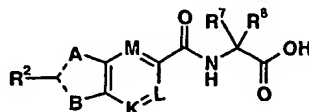
1c

wherein A , R^2 , B , K , L , M , R^7 and R^8 are as defined herein, or a salt, or a derivative

thereof.

In an fourteenth aspect of the invention, there is provided a process for producing compounds of formula I, comprising:

- 5 a) coupling, in a mixture containing an aprotic solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1c:

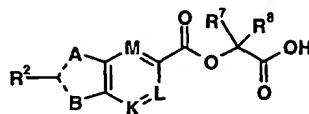


1c

with amine **Q**-NH₂ so as to produce compounds of formula I, wherein **A**, **R**², **B**, **R**⁷, **R**⁸, **Q**, **K**, **L**, and **M** are as defined herein.

10

In an fifteenth aspect of the invention, there is provided an intermediate compound represented by formula 1d:



1d

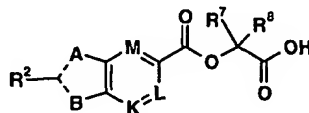
wherein **A**, **R**², **B**, **K**, **L**, **M**, **R**⁷ and **R**⁸ are as defined herein or a salt or a derivative thereof.

15

In a sixteenth aspect of the invention, there is provided a process for producing compounds of formula I, comprising:

- a) coupling, in a mixture containing an appropriate solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1d:

20



1d

with amine **Q**-NH₂ so as to produce compounds of formula I, wherein **A**, **R**², **B**, **R**⁷, **R**⁸, **Q**, **K**, **L**, and **M** are as defined herein.

- 25 In a seventeenth aspect of the invention, there is provided a method of treating or

preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in combination with another anti-HCV agent.

5 DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following definitions apply unless otherwise noted:

As used herein, the terms "(C₁₋₃) alkyl", "(C₁₋₄) alkyl" or "(C₁₋₆) alkyl", either alone or in
10 combination with another radical, are intended to mean acyclic straight or branched chain alkyl radicals containing up to three, four and six carbon atoms respectively. Examples of such radicals include methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl.

15 As used herein, the term "(C₂₋₆) alkenyl", either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight chain radical containing two to six carbon atoms.

As used herein, the term "(C₂₋₆) alkynyl" either alone or in combination with another
20 group, is intended to mean an unsaturated, acyclic straight chain sp hybridized radical containing 2 to six carbon atoms.

As used herein, the term "(C₃₋₇) cycloalkyl", either alone or in combination with
another radical, means a cycloalkyl radical containing from three to seven carbon
25 atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "(C₅₋₇)cycloalkenyl", either alone or in combination with
another radical, means an unsaturated cyclic radical containing five to seven carbon
atoms.

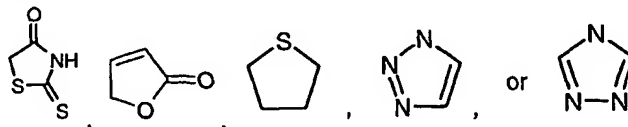
30 As used herein, the term "carboxy protecting group" defines protecting groups that can be used during coupling and are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosures of
35 which are hereby incorporated by reference.

The α -carboxyl group of the C-terminal residue is usually protected as an ester (CPG) that can be cleaved to give the carboxylic acid. Protecting groups that can be used include: 1) alkyl esters such as methyl, trimethylsilylethyl and *t*-butyl, 2) aralkyl
5 esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters.

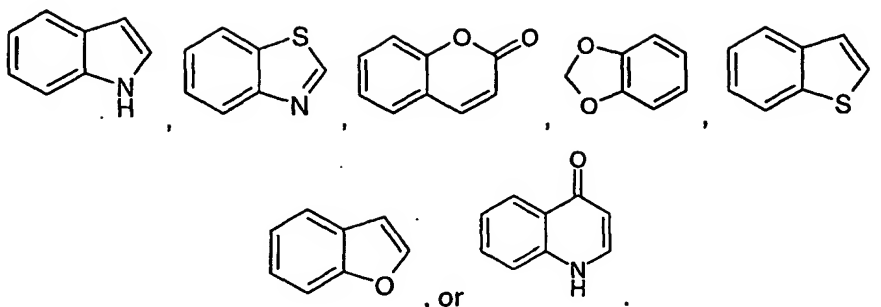
As used herein, the term "aryl", or "6- or 10-membered aryl" either alone or in
10 combination with another radical means aromatic radical containing six or ten carbon atoms, for example phenyl or naphthyl.

As used herein the term heteroatom means O, S or N.

15 As used herein, the term "heterocycle", either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated (including aromatic) heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Furthermore, "heterobicyclic" as used herein, means a heterocycle as defined above
20 fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterocycles include, but are not limited to, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, coumarin, hydantoin, diazepine, 1H-imidazole, isoxazole, thiazole, tetrazole, piperidine, 1,4-dioxane, 4-morpholine, pyridine, pyridine-N-oxide, pyrimidine, thiazolo[4,5-*b*]-pyridine, quinoline, or indole, or the
25 following heterocycles:



As used herein, the term "9- or 10-membered heterobicyclic" or "heterobicyclic" either alone or in combination with another radical, means a heterocycle as defined above
30 fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterobicyclics include, but are not limited to, thiazolo[4,5-*b*]-pyridine, quinoline, or indole, or the following:



As used herein, the term "Het" defines a 5- or 6-membered heterocycle having 1 to 4
 5 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicyclic
 having 1 to 5 heteroatoms wherever possible, selected from O, N and S.

As used herein, the term "halo" means a halogen atom and includes fluorine,
 chlorine, bromine and iodine.

10

As used herein, the term "haloalkyl" is intended to mean an alkyl that is described
 above in which each hydrogen atom may be successively replaced by a halogen
 atom, for example CH_2Br or CF_3 .

15 As used herein, the term "metal halide" is intended to mean any metal that is bonded
 to a halogen atom for use in a metal-catalyzed cross-coupling reaction. Examples of
 such metal halides include, but are not limited to, $-\text{MgCl}$, $-\text{CuCl}$, or $-\text{ZnCl}$ and the like.

As used herein, the term "OH" refers to a hydroxyl group. It is well known to one
 20 skilled in the art that hydroxyl groups may be substituted by functional group
 equivalents. Examples of such functional group equivalents that are contemplated
 by this invention include, but are not limited to, ethers, sulfhydryls, and primary,
 secondary or tertiary amines.

25 As used herein, the term "SH" refers to a sulfhydryl group. It is intended within the
 scope of the present invention that, whenever a "SH" or "SR" group is present, it
 can also be substituted by any other appropriate oxidation state such as SOR , SO_2R ,
 or SO_3R .

30 It is intended that the term "substituted" when applied in conjunction with a radical

having more than one moiety such as C₁₋₆alkyl-aryl, or C₁₋₆alkyl-Het, such substitution applies to both moieties i.e. both the alkyl and aryl or Het moieties can be substituted with the defined substituents.

5 As used herein, the term "COOH" refers to a carboxylic acid group. It is well known to one skilled in the art that carboxylic acid groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, esters, amides, boronic acids or tetrazole.

10

As used herein, the term "functional group equivalent" is intended to mean an element or a substituted derivative thereof, that is replaceable by another element that has similar electronic, hybridization or bonding properties.

15 As used herein, the term "metal catalyst" is intended to mean a metal such as palladium (0) or palladium (2) that is bonded to a leaving group for use in a cross-coupling reaction. Examples of such palladium catalysts include, but are not limited to, Pd(Ph₃)₄, Pd/C, Pd(OAc)₂, PdCl₂, and the like. Alternative metals that can catalyze cross-coupling reactions include, but are not limited to: Ni(acac)₂, Ni(OAc)₂,
20 or NiCl₂.

As used herein, the term "derivative" is intended to mean "detectable label", "affinity tag" or "photoreactive group". The term "detectable label" refers to any group that may be linked to the polymerase or to a compound of the present invention such that
25 when the compound is associated with the polymerase target, such label allows recognition either directly or indirectly of the compound such that it can be detected, measured and quantified. Examples of such "labels" are intended to include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes and affinity tags such as biotin. Such labels
30 are attached to the compound or to the polymerase by well known methods. The term "affinity tag" means a ligand (that is linked to the polymerase or to a compound of the present invention) whose strong affinity for a receptor can be used to extract from a solution the entity to which the ligand is attached. Examples of such ligands include biotin or a derivative thereof, a histidine polypeptide, a
35 polyarginine, an amylose sugar moiety or a defined epitope recognizable by a

specific antibody. Such affinity tags are attached to the compound or to the polymerase by well-known methods.

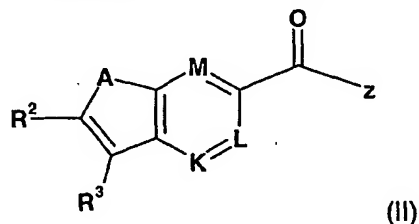
The term "photoreactive group" means a group that is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Examples of such groups include, but are not limited to, benzophenones, azides, and the like.

As used herein, the term "pharmaceutically acceptable salt" includes those derived from pharmaceutically acceptable bases and is non-toxic. Examples of suitable bases include choline, ethanolamine and ethylenediamine. Na⁺, K⁺, and Ca⁺⁺ salts are also contemplated to be within the scope of the invention (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19, incorporated herein by reference).

15 Preferred embodiments

Core:

Preferably, compounds of the present invention have the following formula (II):

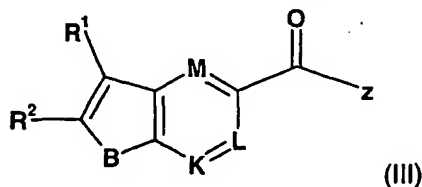


wherein, preferably, A is O, S, or NR¹.

20

More preferably, A is NR¹.

Preferably, compounds of the present invention have the following formula (III):

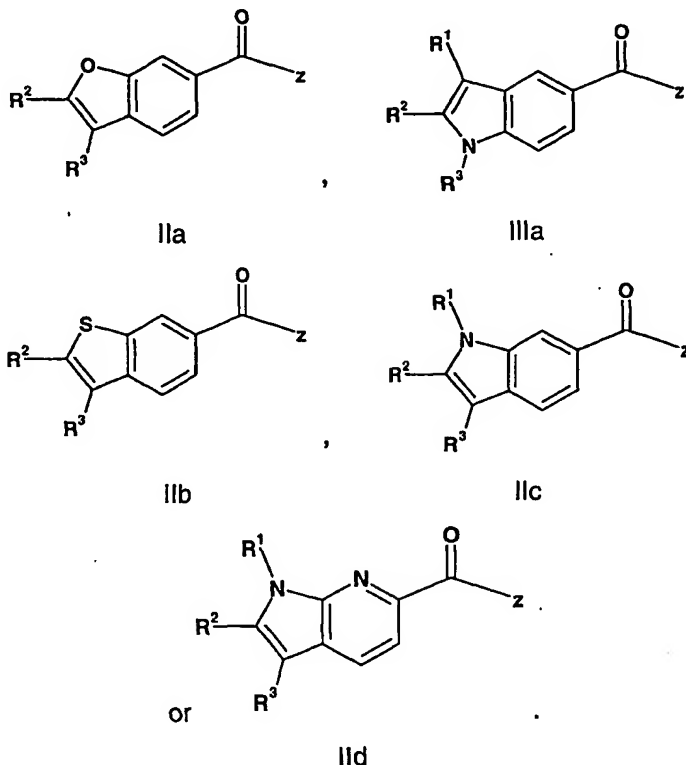


25 wherein, preferably, B is NR³.

With respect to compounds of formula (II) and (III), preferably, M, K and L is CH or

N. More preferably, M, K and L is CH.

More preferably, compounds of the present invention have the following formulae:



R¹:

Preferably **R**¹ is selected from the group consisting of: H or (C₁₋₆)alkyl. More preferably, **R**¹ is H, CH₃, isopropyl, or isobutyl. Even more preferably, **R**¹ is H or CH₃. Most preferably, **R**¹ is CH₃.

R²:

Preferably, R^{22} is $CON(R^{22})_2$, wherein each R^{22} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{5-7}) cycloalkenyl, 6 or 10-membered aryl or Het, or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

or **R**² is selected from: H, halogen, (C₁₋₆)alkyl, haloalkyl, (C₂₋₆)alkenyl, (C₅₋₇)cycloalkenyl, 6 or 10-membered aryl or **Het**; wherein each of said alkyl, haloalkyl, (C₂₋₆)alkenyl, (C₅₋₇)cycloalkenyl, aryl or **Het** is optionally substituted with **R**²⁰, wherein

R²⁰ is defined as:

- 1 to 4 substituents selected from: halogen, NO₂, cyano, azido, C(=NH)NH₂, C(=NH)NH(C₁₋₆)alkyl or C(=NH)NHCO(C₁₋₆)alkyl; or
- 1 to 4 substituents selected from:
 - 5 **a)** (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with **R¹⁵⁰**;
 - b)** **OR¹⁰⁴** wherein **R¹⁰⁴** is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with **R¹⁵⁰**;
 - 10 **c)** **OCOR¹⁰⁵** wherein **R¹⁰⁵** is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with **R¹⁵⁰**;
 - d)** **SR¹⁰⁸**, **SO₂N(R¹⁰⁸)₂** or **SO₂N(R¹⁰⁸)C(O)R¹⁰⁸** wherein each **R¹⁰⁸** is
 - 15 independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or both **R¹⁰⁸** are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with **R¹⁵⁰**;
 - 20 **e)** **NR¹¹¹R¹¹²** wherein **R¹¹¹** is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, and **R¹¹²** is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)**Het**, **COOR¹¹⁵** or **SO₂R¹¹⁵** wherein **R¹¹⁵** is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both **R¹¹¹** and **R¹¹²** are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with **R¹⁵⁰**;
 - 25 **f)** **NR¹¹⁶COR¹¹⁷** wherein **R¹¹⁶** and **R¹¹⁷** is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with **R¹⁵⁰**;
 - 30 **g)** **NR¹¹⁸CONR¹¹⁹R¹²⁰**, wherein **R¹¹⁸**, **R¹¹⁹** and **R¹²⁰** is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with **R¹⁵⁰**;

- ₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or **R**¹¹⁸ is covalently bonded to **R**¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or **R**¹¹⁹ and **R**¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
- 5 said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with **R**¹⁵⁰;
- h) NR**¹²¹**COCOR**¹²² wherein **R**¹²¹ and **R**¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁵⁰;
- 10 or **R**¹²² is **OR**¹²³ or **N(R**¹²⁴**)**₂ wherein **R**¹²³ and each **R**¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or **R**¹²⁴ is OH or O(C₁₋₆alkyl) or both **R**¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with **R**¹⁵⁰;
- 15 **i) COR**¹²⁷ wherein **R**¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁵⁰;
- 20 **j) COOR**¹²⁸ wherein **R**¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁵⁰;
- 25 **k) CONR**¹²⁹**R**¹³⁰ wherein **R**¹²⁹ and **R**¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both **R**¹²⁹ and **R**¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with **R**¹⁵⁰;
- 30 **l) aryl, Het, (C1-6alkyl)aryl or (C1-6alkyl)Het**, all of which being optionally substituted with **R**¹⁵⁰, wherein **R**¹⁵⁰ is preferably:
- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
 - 1 to 3 substituents selected from:

- a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;
- b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said alkyl or cycloalkyl optionally substituted with R¹⁶⁰;
- 5 d) SR¹⁰⁸, SO₃H, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het and heterocycle being optionally substituted with R¹⁶⁰;
- 10 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, or (C₃₋₇)cycloalkyl, and R¹¹² is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁶⁰;
- 15 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl said (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl being optionally substituted with R¹⁶⁰;
- 20 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, and heterocycle being optionally substituted with R¹⁶⁰;
- 25 h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R¹⁶⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁶⁰;
- 30 i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said alkyl

and cycloalkyl being optionally substituted with R^{160} ;

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, said (C_{1-6}) alkyl and (C_{3-7}) cycloalkyl being optionally substituted with R^{160} ; and

5 k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160} ;

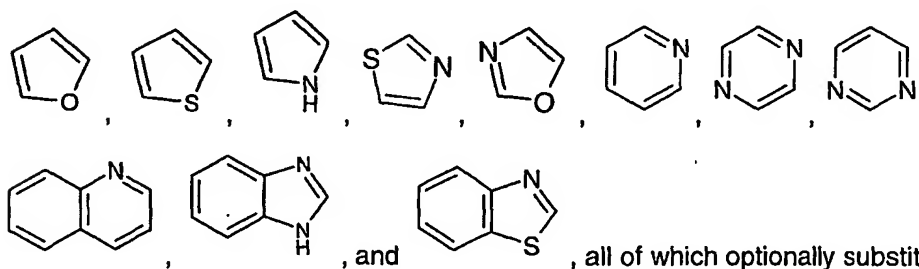
10 wherein R^{160} is defined as 1 or 2 substituents selected from: halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, R^2 is selected from: aryl or Het, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, N_3 , or

- 20 a) (C_{1-6}) alkyl optionally substituted with OH, $O(C_{1-6})$ alkyl or $SO_2(C_{1-6})$ alkyl);
- b) (C_{1-6}) alkoxy;
- 25 e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or R^{112} is 6- or 10-membered aryl, Het, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-Het; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, Het, alkyl-aryl or alkyl-Het; being optionally substituted with halogen or:
- 30 - OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6}) alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle;
- f) $NHCOR^{117}$ wherein R^{117} is (C_{1-6}) alkyl, $O(C_{1-6})$ alkyl or $O(C_{3-7})$ cycloalkyl;

- i) CO-aryl; and
- k) CONH_2 , $\text{CONH}(\text{C}_{1-6}\text{alkyl})$, $\text{CON}(\text{C}_{1-6}\text{alkyl})_2$, CONH-aryl , or $\text{CONHC}_{1-6}\text{alkyl aryl}$.
- 5 Still, more preferably, R^2 is aryl or Het, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, or
- a) $(\text{C}_{1-6})\text{alkyl}$ optionally substituted with OH, $\text{O}(\text{C}_{1-6})\text{alkyl}$ or $\text{SO}_2(\text{C}_{1-6}\text{alkyl})$;
- 10 b) $(\text{C}_{1-6})\text{alkoxy}$; and
- e) $\text{NR}^{111}\text{R}^{112}$ wherein both R^{111} and R^{112} are independently H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, or R^{112} is 6- or 10-membered aryl, Het, $(\text{C}_{1-6})\text{alkyl-aryl}$ or $(\text{C}_{1-6})\text{alkyl-Het}$; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-
- 15 containing heterocycle, each of said alkyl, cycloalkyl, aryl, Het, alkyl-aryl or alkyl-Het; or being optionally substituted with halogen or:
- OR^{2h} or $\text{N}(\text{R}^{2h})_2$, wherein each R^{2h} is independently H, $(\text{C}_{1-6})\text{alkyl}$, or both R^{2h} are covalently bonded together and to the
- 20 containing heterocycle.

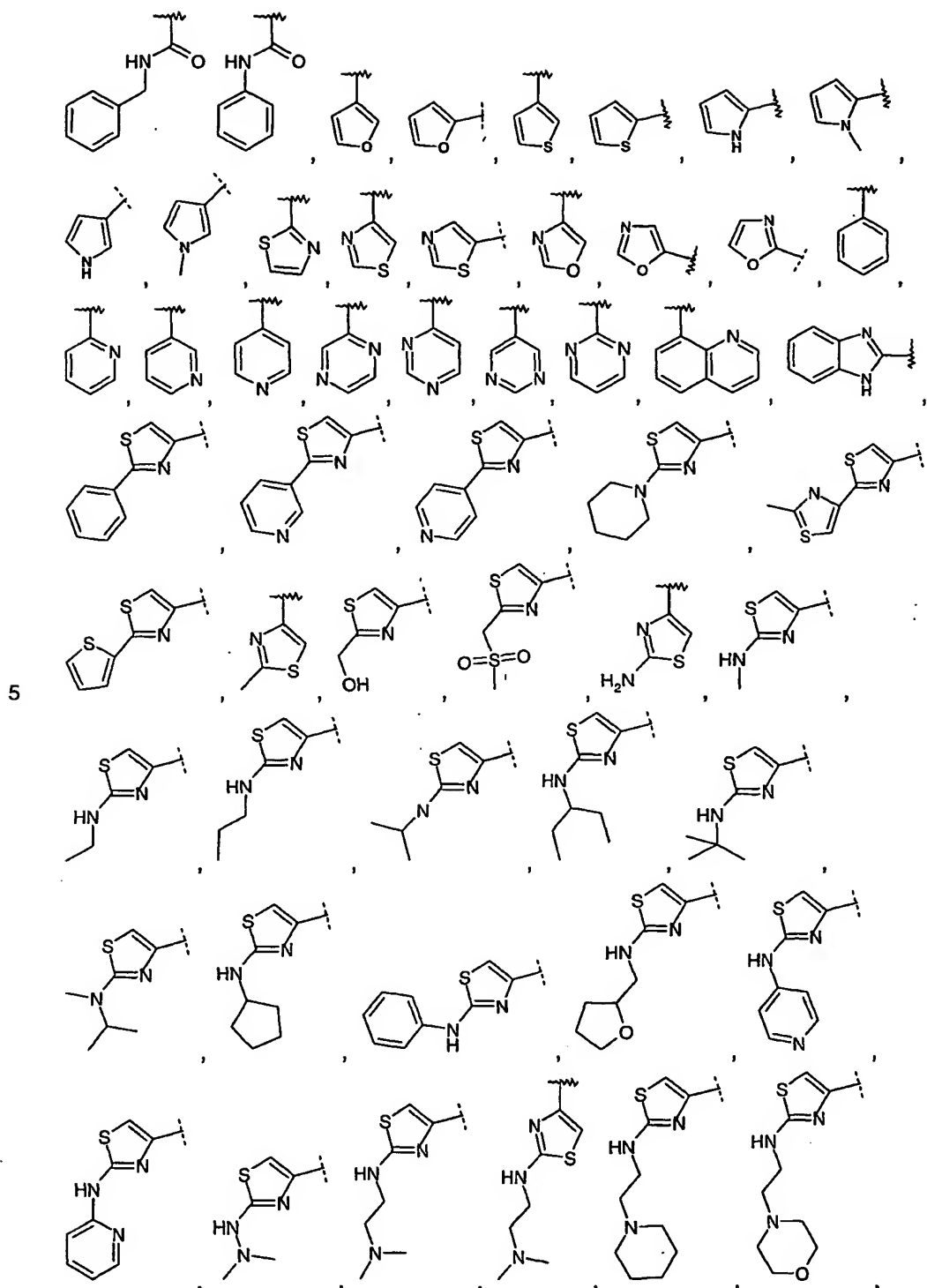
Even more preferably, R^2 is phenyl or a heterocycle selected from:

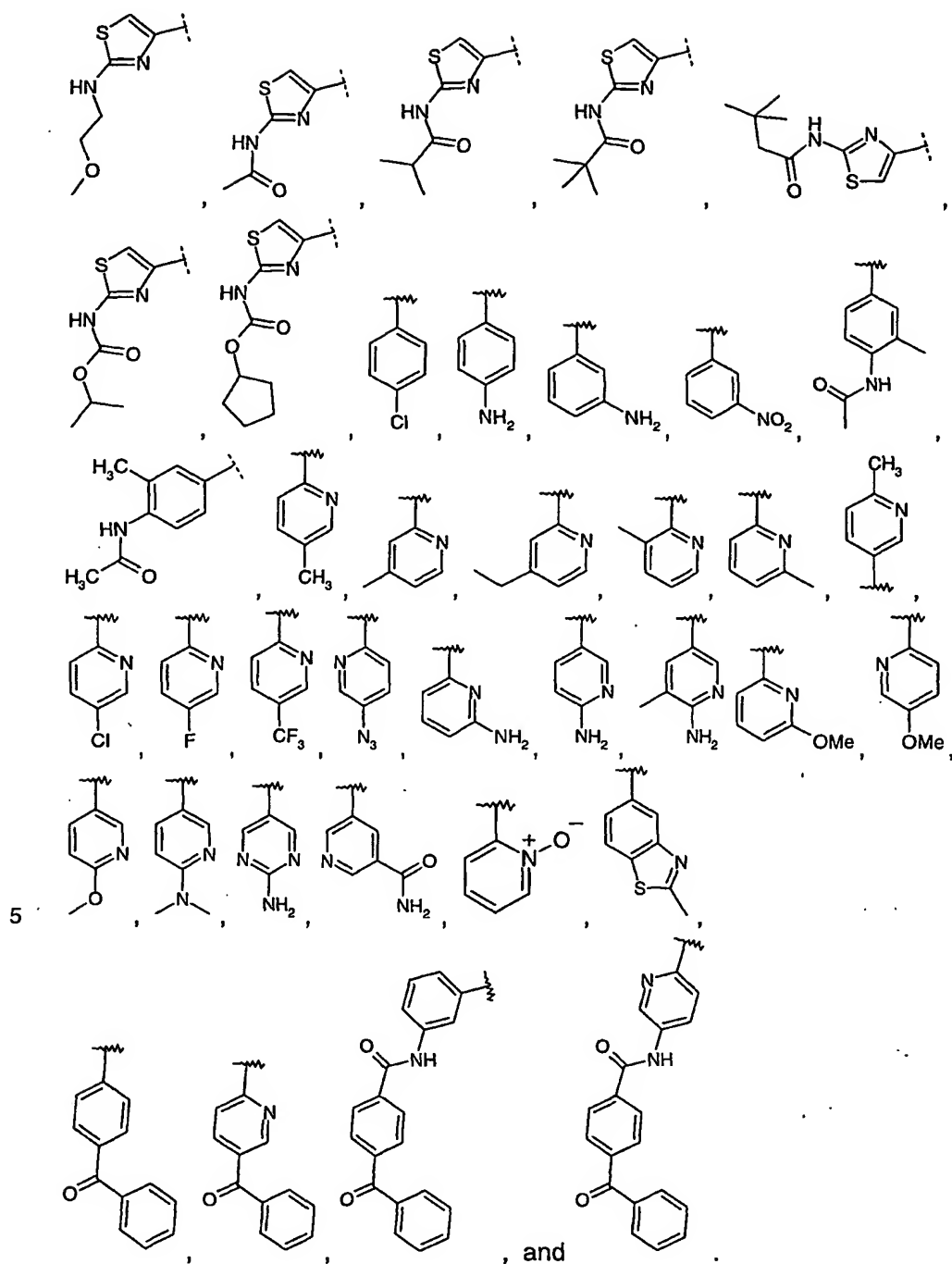


25 as defined above.

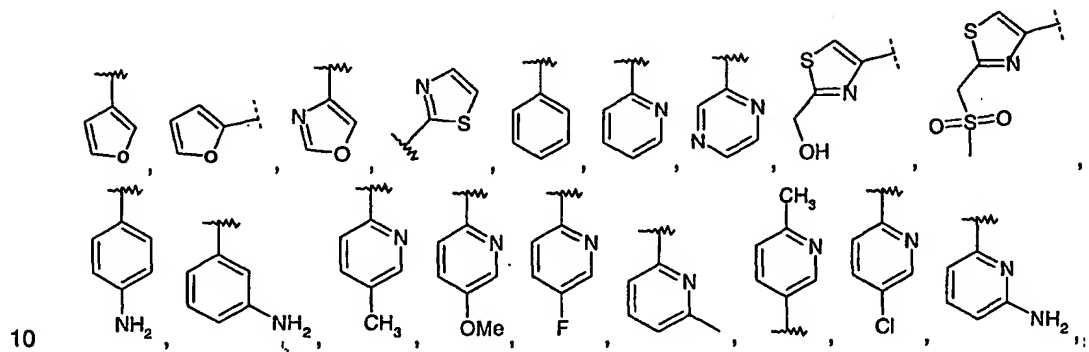
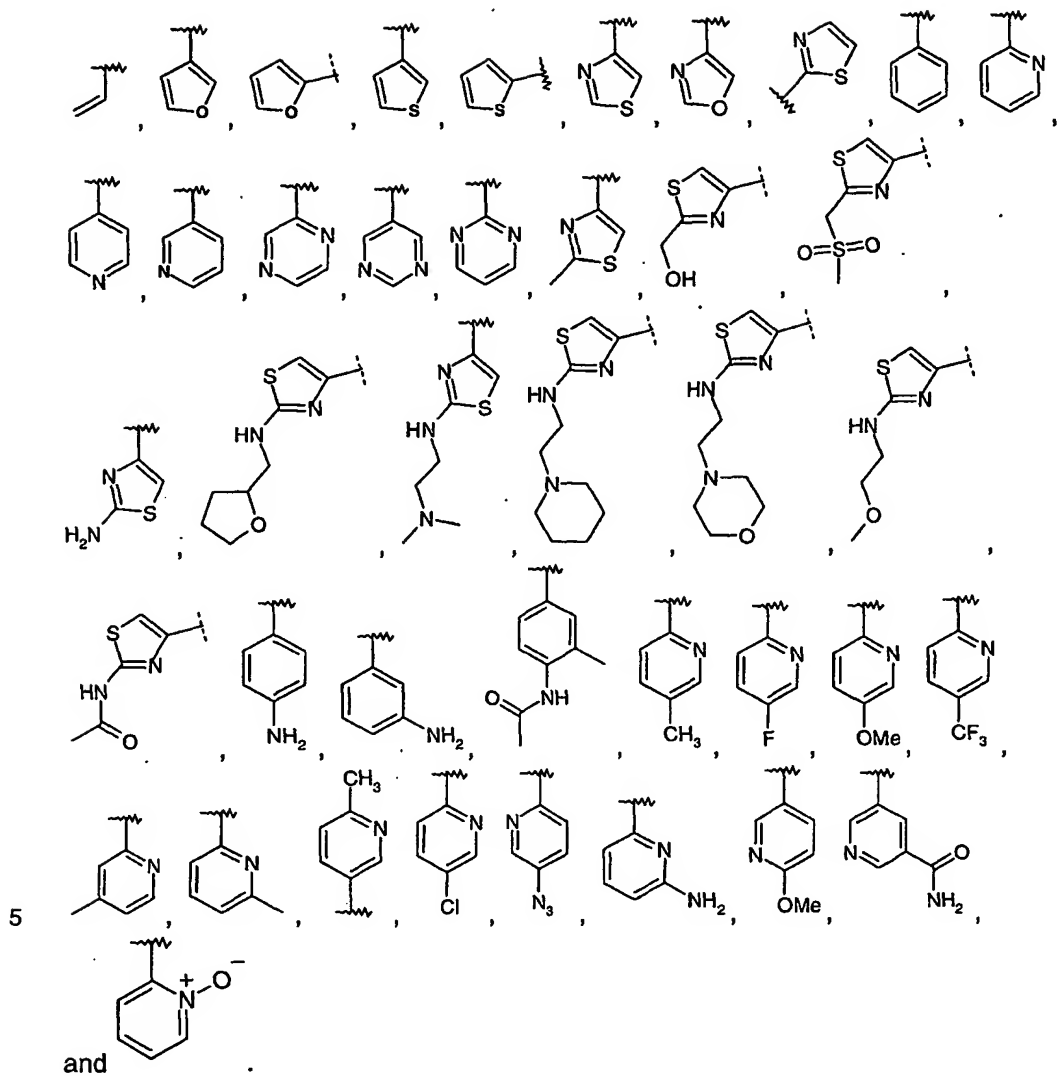
Even more preferably, R^2 is selected from the group consisting of:

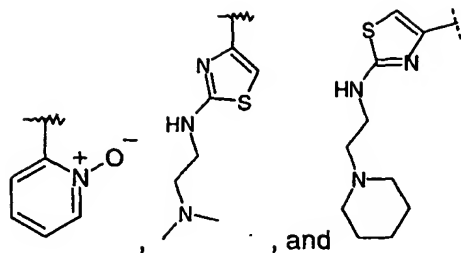
H, Br, CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONH_2 , CH=CH_2 ,





Still more preferably, R^2 is selected from:



**R³:**

Preferably, **R³** is selected from (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkenyl, (C₆₋₁₀)bicycloalkyl,
 5 (C₆₋₁₀)bicycloalkenyl, 6- or 10-membered aryl, or **Het**. More preferably, **R³** is (C₃₋₇)cycloalkyl. Most preferably, **R³** is cyclopentyl, or cyclohexyl.

Y:

Preferably **Y¹** is O.

10

Z:

Preferably, **Z** is **OR⁶** wherein **R⁶** is (C₁₋₆alkyl)aryl substituted with:

- 1 to 4 substituents selected from:

- a) (C₁₋₆)alkyl substituted with **R^{150a}**, haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇
 15 spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with **R¹⁵⁰**, wherein **R^{150a}** is the same as **R¹⁵⁰** but is not **COOR^{150b}**, **N(R^{150b})₂**, **NR^{150b}C(O)R^{150b}**, **OR^{150b}**, **SR^{150b}**, **SO₂R^{150b}**, **SO₂N(R^{150b})₂**, wherein **R^{150b}** is H
 20 or unsubstituted C₁₋₆alkyl;
- b) **OR¹⁰⁴** wherein **R¹⁰⁴** is (C₁₋₆alkyl) substituted with **R¹⁵⁰**, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with **R¹⁵⁰**;
- 25 d) **SR^{108a}**, **SO₂N(R^{108a})₂** or **SO₂N(R¹⁰⁸)C(O)R¹⁰⁸** wherein each **R¹⁰⁸** is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both **R¹⁰⁸** are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with
 30

- R^{150} , wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6} alkyl;
- e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)Het, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, and R^{115a} is the same as R^{115} but is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, or heterocycle being optionally substituted with R^{150} ;
- f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6}) alkyl substituted with R^{150} , (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, said (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het being optionally substituted with R^{150} ;
- g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het or heterocycle being optionally substituted with R^{150} ;
- h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or C_{1-6} alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, or R^{124} is OH or $O(C_{1-6})$ alkyl or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het and heterocycle being optionally substituted with R^{150} ;
- i) $COOR^{128}$ wherein R^{128} is (C_{1-6}) alkyl substituted with R^{150} , (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, said (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl and (C_{1-6}) alkyl)Het

₆alkyl)Het being optionally substituted with R^{150} ;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R^{150} ;

l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R^{150} ; wherein R^{150} is:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R^{160} ;

b) OR^{104} wherein R^{104} is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R^{160} ;

d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R^{160} ;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R^{112} is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are

attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;

5 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

10 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

15 h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

20 i) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰; and

25 j) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and

heterocycle being optionally substituted with R^{160} ;

wherein, R^{160} is defined as 1 or 2 substituents selected from:
 tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, SO_3H ,
 SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or
 $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

5

More preferably, Z is OR^6 wherein R^6 is $(C_{1-6}alkyl)aryl$ substituted with:

- 1 to 4 substituents selected from:

- a) $(C_{1-6}alkyl)$ substituted with R^{150a} , haloalkyl, $(C_{3-7}cycloalkyl)$, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, $(C_{2-6}alkenyl)$, $(C_{2-6}alkynyl)$, $(C_{1-6}alkyl-(C_{3-7}cycloalkyl))$, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150} , wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b} , SR^{150b} , SO_2R^{150b} , $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted $C_{1-6}alkyl$;
- b) OR^{104} wherein R^{104} is $(C_{1-6}alkyl)$ substituted with R^{150} , $(C_{3-7}cycloalkyl)$, or $(C_{1-6}alkyl-(C_{3-7}cycloalkyl))$, aryl, Het, $(C_{1-6}alkyl)aryl$ or $(C_{1-6}alkyl)Het$, said cycloalkyl, aryl, Het, $(C_{1-6}alkyl)aryl$ or $(C_{1-6}alkyl)Het$ being optionally substituted with R^{150} ;
- d) SO_3H , $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, $(C_{1-6}alkyl)$ and aryl, said alkyl and aryl being optionally substituted with R^{150} , wherein R^{108a} is the same as R^{108} but is not H or unsubstituted $C_{1-6}alkyl$;
- e) $NR^{111}R^{112}$ wherein R^{111} is H, $(C_{1-6}alkyl)$, $(C_{3-7}cycloalkyl)$ or $(C_{1-6}alkyl-(C_{3-7}cycloalkyl))$, aryl, Het, $(C_{1-6}alkyl)aryl$ or $(C_{1-6}alkyl)Het$, and R^{112} is H, $(C_{1-6}alkyl)$, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, $(C_{1-6}alkyl)$ or $(C_{1-6}alkyl)aryl$, and R^{115a} is $C_{1-6}alkyl$ substituted with R^{150} or $(C_{1-6}alkyl)aryl$, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, $(C_{1-6}alkyl)aryl$ or $(C_{1-6}alkyl)Het$, or heterocycle being optionally substituted with R^{150} ;
- f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each $(C_{1-6}alkyl)$ substituted with R^{150} , $(C_{3-7}cycloalkyl)$, aryl, Het, said $(C_{3-7}cycloalkyl)$, aryl, Het being optionally

30

substituted with R^{150} ;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, aryl, Het, said alkyl, aryl and Het being optionally substituted with R^{150} ;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or C_{1-6} alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}) alkyl, aryl or Het, or R^{124} is OH or $O(C_{1-6})$ alkyl, said alkyl, aryl and Het being optionally substituted with R^{150} ;

j) $COOR^{128}$ wherein R^{128} is (C_{1-6}) alkyl substituted with R^{150} ;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, aryl or Het, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, said alkyl, aryl and Het being optionally substituted with R^{150} ;

l) aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, all of which being optionally substituted with R^{150} ; wherein R^{150} is:

- 1 to 3 substituents selected from: halogen or azido; or

- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6}) alkenyl, all of which optionally substituted with R^{160} ;

b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, aryl or Het, and R^{112} is H, (C_{1-6}) alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6}) alkyl, said alkyl, aryl or Het being optionally substituted with R^{160} ;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6}) alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}) alkyl, aryl or Het, or R^{124} is OH or $O(C_{1-6})$ alkyl, said alkyl, aryl and Het being

optionally substituted with R^{160} ;

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6}) alkyl optionally substituted with R^{160} ; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, SO_3H , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

Even more preferably, Z is OR^6 wherein R^6 is (C_{2-6}) alkenyl, (C_{1-6}) alkyl-Het, wherein said alkenyl or alkyl-Het, is optionally substituted with R^{60} , wherein preferably R^{60} is:

- 1 to 4 substituents selected from: halogen; or

- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-8}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} ;

b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het being optionally substituted with R^{150} ;

d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het or heterocycle being optionally substituted with R^{150} ;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)Het, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het.

₆alkyl)Het, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R^{150} ;

5 f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R^{150} ;

10 g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R^{150} ;

15 h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C₁₋₆alkyl optionally substituted with R^{150} , and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R^{124} is OH or O(C₁₋₆alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R^{150} ;

20 i) COR^{127} wherein R^{127} is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R^{150} ;

25 j) $COOR^{128}$ wherein R^{128} is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R^{150} ;

30 k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated

heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰, wherein R¹⁵⁰ is defined as:

- 5 - 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:
 - a)** (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;
 - 10 **b)** OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;
 - d)** SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;
 - 15 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;
 - 20 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted
 - 25
 - 30

with R^{160} ;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or heterocycle being optionally substituted with R^{160} ;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C₁₋₆)alkyl optionally substituted with R^{160} , and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or R^{124} is OH or O(C₁₋₆)alkyl or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het and heterocycle being optionally substituted with R^{160} ;

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl and (C₁₋₆)alkyl)Het being optionally substituted with R^{160} ; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)Het and heterocycle being optionally substituted with R^{160} ;

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, $COOR^{161}$, SO_3H , SR^{161} , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H,

(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both **R**¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

5

Even more preferably, **R**⁶⁰ is:

- 1 to 4 substituents selected from: halogen; or

- 1 to 4 substituents selected from:

- 10 a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with **R**¹⁵⁰;
- b) OR¹⁰⁴ wherein **R**¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with
- 15 **R**¹⁵⁰;
- d) SO₃H, SO₂N(**R**¹⁰⁸)₂ or SO₂N(**R**¹⁰⁸)C(O)**R**¹⁰⁸ wherein each **R**¹⁰⁸ is independently H, (C₁₋₆)alkyl or aryl, said alkyl and aryl being optionally substituted with **R**¹⁵⁰;
- 20 e) NR¹¹¹**R**¹¹² wherein **R**¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, and **R**¹¹² is H, (C₁₋₆)alkyl, COOR¹¹⁵ or SO₂**R**¹¹⁵ wherein **R**¹¹⁵ is (C₁₋₆)alkyl or (C₁₋₆)alkyl)aryl, or both **R**¹¹¹ and **R**¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being
- 25 optionally substituted with **R**¹⁵⁰;
- f) NR¹¹⁶COR¹¹⁷ wherein **R**¹¹⁶ and **R**¹¹⁷ is each (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl or **Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl or **Het** being optionally substituted with **R**¹⁵⁰;
- g) NR¹¹⁸CONR¹¹⁹**R**¹²⁰, wherein **R**¹¹⁸, **R**¹¹⁹ and **R**¹²⁰ is each H, (C₁₋₆)alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with **R**¹⁵⁰;
- 30 h) NR¹²¹COCOR¹²² wherein **R**¹²¹ is H or (C₁₋₆)alkyl, and **R**¹²² is OR¹²³ or N(**R**¹²⁴)₂ wherein **R**¹²³ and each **R**¹²⁴ is independently H, (C₁₋₆)alkyl, aryl or **Het**, or **R**¹²⁴ is OH or O(C₁₋₆)alkyl, said alkyl, aryl and **Het** being optionally substituted with **R**¹⁵⁰;

- j) COOR¹²⁸ wherein R¹²⁸ is H or (C₁₋₆)alkyl optionally substituted with R¹⁵⁰;
- k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R¹⁵⁰;
- l) aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, all of which being optionally substituted with R¹⁵⁰, wherein R¹⁵⁰ is defined as:
- 1 to 3 substituents selected from: halogen; or
 - 1 to 3 substituents selected from:
 - a) (C₁₋₆) alkyl or haloalkyl, (C₂₋₆)alkenyl, all of which optionally substituted with R¹⁶⁰;
 - b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R¹⁶⁰;
 - d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R¹⁶⁰;
 - e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, aryl or Het, and R¹¹² is H, (C₁₋₆)alkyl, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl or aryl, said alkyl, aryl and Het being optionally substituted with R¹⁶⁰;
 - f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R¹⁶⁰;
 - g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R¹⁶⁰;
 - h) NR¹²¹COCOR¹²² wherein R¹²¹ is H or (C₁₋₆)alkyl optionally substituted with R¹⁶⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, aryl or Het, or R¹²⁴ is OH or O(C₁₋₆)alkyl, said alkyl, aryl and Het being optionally substituted with R¹⁶⁰;
 - j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H or (C₁₋₆)alkyl optionally substituted with R¹⁶⁰; and
 - k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R¹⁶⁰;
- wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H,

5 SR^{161} , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Most preferably, Z is $N(R^{6a})R^6$ wherein R^{6a} is H or C_{1-6} alkyl. More preferably, R^{6a} is H.

10 Preferably, R^6 is (C_{2-6}) alkenyl, aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, wherein said alkenyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, OPO_3H , NO_2 , cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$ alkyl or $C(=NH)NHCO(C_{1-6})$ alkyl; or

- 1 to 4 substituents selected from:

15 a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-8}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} ;

b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said alkyl, cycloalkyl, 20 aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;

d) SR^{108} , $SO_2NH(C_{1-6})$ alkyl or $SO_2NHC(O)C_{1-6}$ alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl, 25 (C_{1-6}) alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, or 30 heterocycle being optionally substituted with R^{150} ;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or

(C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁵⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R¹⁵⁰, wherein, preferably, R¹⁵⁰ is selected from:

- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or

- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl

optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl,

5 (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

10 **d)** SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said
15 alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁶⁰;

e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein
20 R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said
25 alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;

f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted
30 with R¹⁶⁰;

g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹¹⁹ and R¹²⁰ are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

5 h) NR¹²¹COCOR¹²² wherein R¹²¹ is H or (C₁₋₆)alkyl optionally substituted with R¹⁶⁰; and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆)alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

10 j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl and (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁶⁰; and

15 k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

20 wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both R¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, R⁶ is (C₂₋₆)alkenyl, aryl, **Het**, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-**Het**, wherein

said alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, NO₂, cyano, azido; or
- 1 to 4 substituents selected from:

- a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰;
- b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁵⁰;
- d) SH, S(C₁₋₆)alkyl, SO₃H, SO₂NH(C₁₋₆)alkyl or SO₂NHC(O)C₁₋₆alkyl;
- e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl being optionally substituted with R¹⁵⁰;
- g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R¹⁵⁰;
- h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, said alkyl, cycloalkyl being optionally substituted with R¹⁵⁰, or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl) or (C₃₋₇)cycloalkyl, or R¹²⁴ is OH or O(C₁₋₆)alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁵⁰;
- i) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋

₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰, wherein, preferably, R¹⁵⁰ is selected from:

- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

d) SH, S(C₁₋₆alkyl), SO₃H, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;

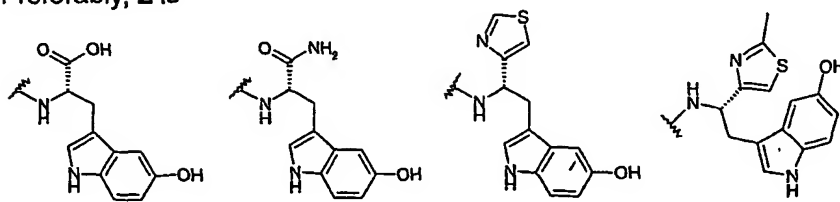
- 5 f) $\text{NR}^{116}\text{COR}^{117}$ wherein R^{116} and R^{117} is each H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, said $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ being optionally substituted with R^{160} ;
- 10 g) $\text{NR}^{118}\text{CONR}^{119}\text{R}^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ or heterocycle being optionally substituted with R^{160} ;
- 15 h) $\text{NR}^{121}\text{COCOR}^{122}$ wherein R^{121} is H, $(\text{C}_{1-6})\text{alkyl}$ optionally substituted with R^{160} ; and R^{122} is OR^{123} or $\text{N}(\text{R}^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or R^{124} is OH or O $(\text{C}_{1-6}\text{alkyl})$ or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ and heterocycle being optionally substituted with R^{160} ;
- 20 i) tetrazole, COOR^{128} wherein R^{128} is H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, said $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ and $(\text{C}_{1-6}\text{alkyl})\text{Het}$ being optionally substituted with R^{160} ;
- 25 and
- k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$, $(\text{C}_{1-6}\text{alkyl})\text{Het}$ and heterocycle being optionally substituted with R^{160} ;
- 30 wherein, preferably, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, $\text{C}_{1-6}\text{alkyl}$, haloalkyl,

COOR^{161} , SO_3H , $\text{SO}_2\text{R}^{161}$, OR^{161} , $\text{N}(\text{R}^{162})_2$, $\text{SO}_2\text{N}(\text{R}^{162})_2$, $\text{NR}^{162}\text{COR}^{162}$ or $\text{CON}(\text{R}^{162})_2$, wherein R^{161} and each R^{162} is independently H or (C_{1-6}) alkyl.

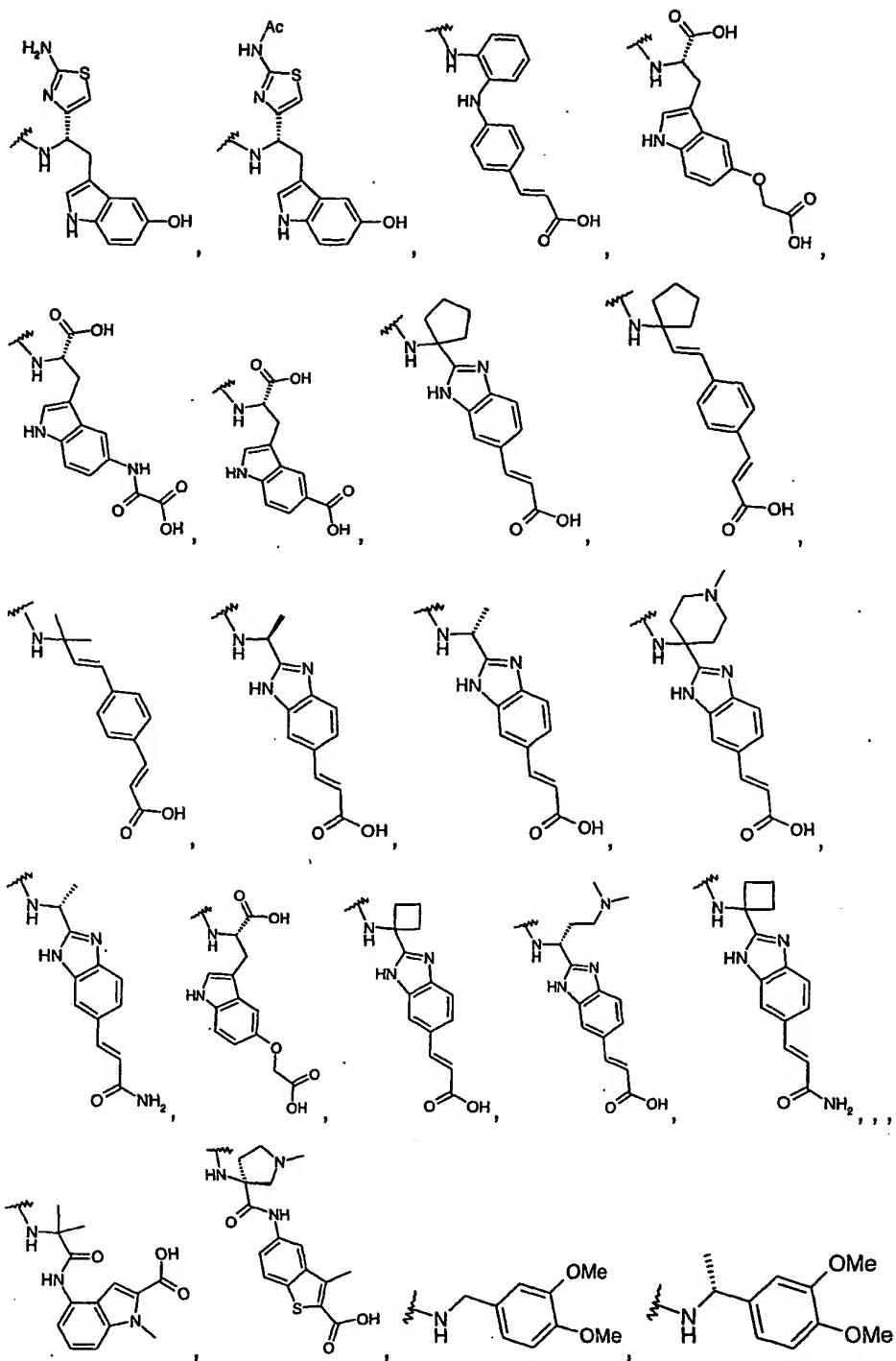
- 5 Most preferably, R^6 is C_{2-6} alkenyl, phenyl, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-Het, wherein said alkenyl, phenyl and the alkyl portion of said alkyl-aryl, or alkyl-Het, are optionally substituted with 1 to 3 of:

- a) (C_{1-6}) alkyl C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, all of which optionally substituted with C_{1-6} alkyl or C_{1-6} alkoxy;
 10 NH_2 , $\text{NH}(\text{Me})$ or $\text{N}(\text{Me})_2$
 e) NHR^{112} wherein R^{112} is aryl, Het, $(\text{C}_{1-6}$ alkyl)aryl, $(\text{C}_{1-6}$ alkyl)Het, said aryl, Het, $(\text{C}_{1-6}$ alkyl)aryl or $(\text{C}_{1-6}$ alkyl)Het, being optionally substituted with R^{150} ;
 j) COOH ;
 k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, $(\text{C}_{1-6}$ alkyl)aryl or (C_{1-6}) alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, $(\text{C}_{1-6}$ alkyl)aryl, and (C_{1-6}) alkyl)Het being optionally substituted with R^{150} ;
 15 l) phenyl or Het, both optionally substituted with R^{150} , wherein, preferably, R^{150} is selected from:
 20 - 1 or 2 substituents selected from: halogen, NO_2 , cyano or azido;
 - 1 or 2 substituents selected from:
 a) (C_{1-6}) alkyl or (C_{2-6}) alkenyl, both optionally substituted with COOH or CONH_2 ;
 b) OR^{104} wherein R^{104} is H or (C_{1-6}) alkyl optionally substituted with
 25 COOH ;
 h) NHCOCOOH ;
 j) COOH ; and
 k) CONH_2 .

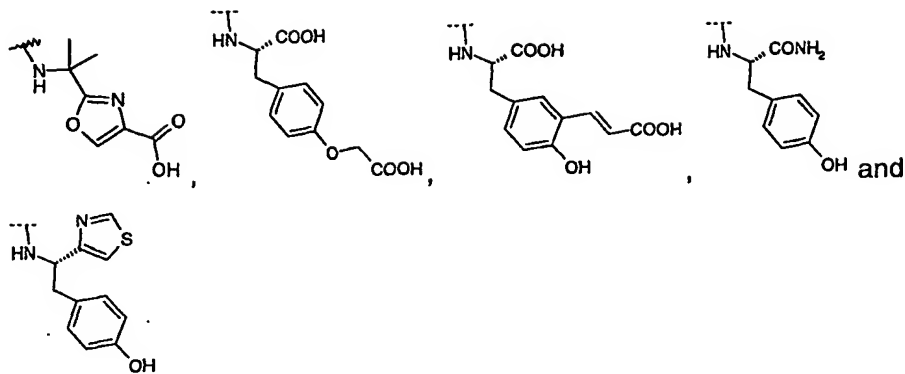
- 30 Preferably, Z is



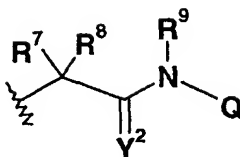
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**Diamides:**

- 5 Most preferably, R^6 is:



- wherein, preferably, R^7 and R^8 are each independently H, (C₁₋₆)alkyl, haloalkyl, (C₃₋₇)cycloalkyl, 6- or 10-membered aryl, Het, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-Het, wherein said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-Het are optionally substituted with R^{70} ; or
- 10 R^7 and R^8 are covalently bonded together to form second (C₃₋₇)cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when Z is N(R^{6a}) R^6 , either of R^7 or R^8 is covalently bonded to R^{6a} to form a nitrogen-containing 5- or 6-membered heterocycle; wherein, preferably, R^{70} is
- 15 selected from:

- 1 to 4 substituents selected from: halogen, NO₂, cyano, azido; or

- 1 to 4 substituents selected from:

- a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R^{150} ;
- 20 b) OR¹⁰⁴ wherein R^{104} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het being optionally substituted with R^{150} ;
- 25 d) SR¹⁰⁸, SO₂N(R^{108})₂ or SO₂N(R^{108})C(O) R^{108} wherein each R^{108} is

- independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 5 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 10 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 15 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 20 h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁵⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆)alkyl or both R¹²⁴ are covalently bonded
- 25
- 30

together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

- 5 i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 10 k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated
- 15 heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;
- l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰, wherein, preferably, R¹⁵⁰ is selected from:

- 20 - 1 to 3 substituents selected from: halogen, NO₂, cyano, azido; or
- 1 to 3 substituents selected from:
- a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, all of which optionally substituted with R¹⁶⁰;
- 25 b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R¹⁶⁰;
- d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ wherein R¹⁰⁸ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R¹⁶⁰;
- 30 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, and R¹¹² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl,

cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;

f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl being optionally substituted with R¹⁶⁰;

g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R¹⁶⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R¹⁶⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁶⁰;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl being optionally substituted with R¹⁶⁰; and

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁶⁰;

wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂ or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H or (C₁₋₆)alkyl.

More preferably, R⁷ and R⁸ are each independently H, (C₁₋₆)alkyl, haloalkyl, (C₃₋₇)cycloalkyl, 6- or 10-membered aryl, Het, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-Het, all of which optionally substituted with from 1 to 4 substituents selected from halogen or:

a) (C₁₋₆)alkyl; and

- b) $N(R^{8a'})_2$, COR^{8a} , or $SO_2R^{8a''}COOR^{8a}$, $COCOOR^{8a}$, $CON(R^{8a'})_2$, $COCON(R^{8a'})_2$, wherein each R^{8a} or $R^{8a'}$ are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or each $R^{8a'}$ are independently covalently bonded together and to the nitrogen to which they are both bonded to form a 5, 6 or 7-membered saturated heterocycle; or $R^{8a''}$ is independently (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl.

or R^7 and R^8 are covalently bonded together to form (C_{3-7}) cycloalkyl, 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S.

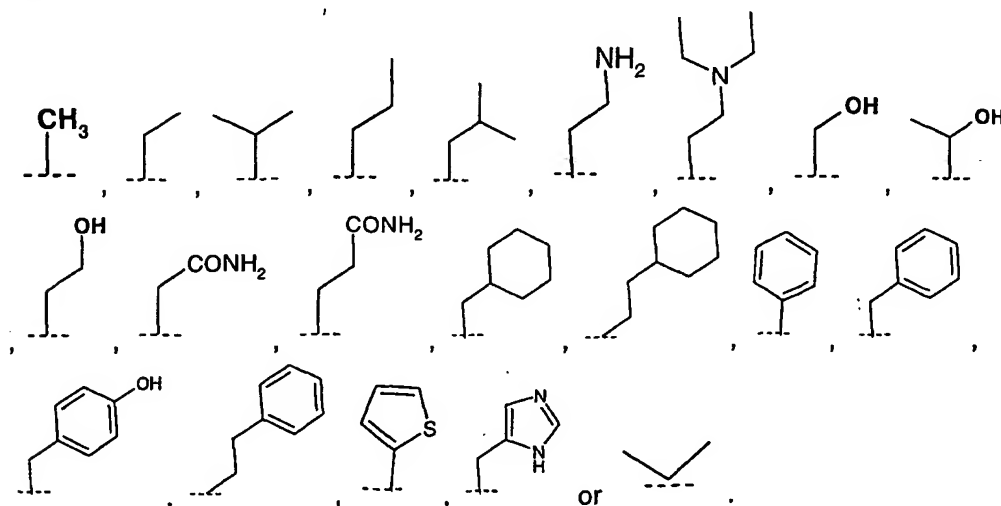
Most preferably, R^7 and R^8 are each independently H, (C_{1-6}) alkyl, haloalkyl, (C_{3-7}) cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**; or R^7 and R^8 are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide;

wherein said alkyl, haloalkyl, (C_{3-7}) cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide are optionally monosubstituted with substituents selected from:

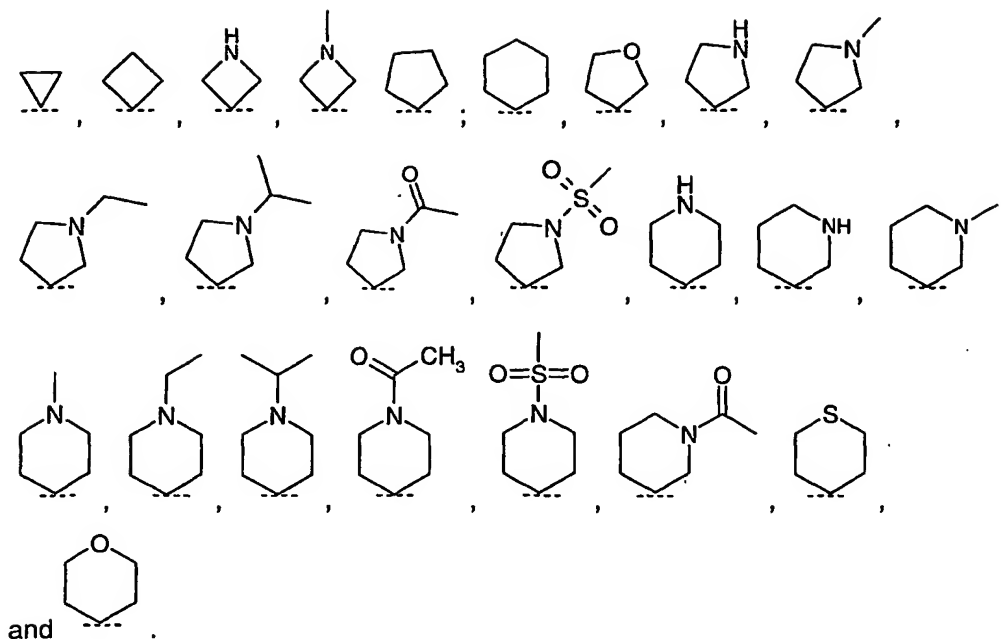
a) (C_{1-6}) alkyl; and

c) NH_2 , $N(CH_2CH_3)_2$, $COCH_3$, or SO_2CH_3 .

Even more preferably, R^7 and R^8 are selected from:

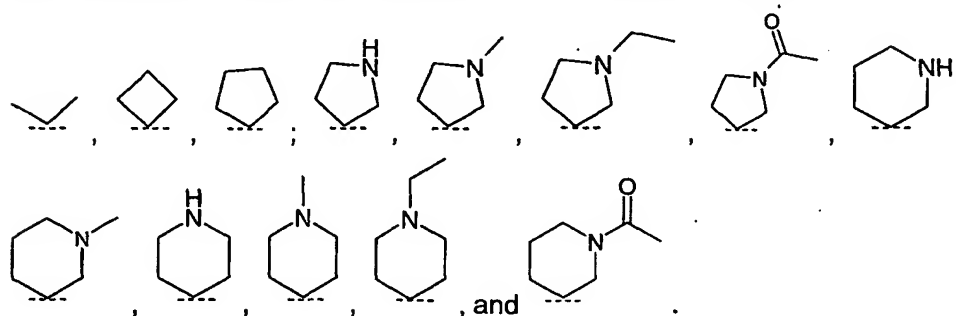


R^7 and R^8 together form:



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Most preferably, R^7 and R^8 are selected from the group consisting of:

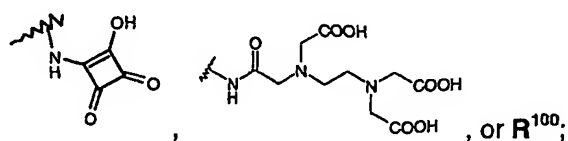


10 R⁹:

Preferably R^9 is H; or R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle. More preferably, R^9 is H.

Q:

15 Preferably, **Q** is a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)-Het, all of which being optionally substituted with:



wherein R^{100} is:

- 1 to 4 substituents selected from: halogen, NO_2 , cyano or azido; or

- 1 to 4 substituents selected from:

- a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} ;
- b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;
- d) SR^{108} wherein R^{108} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, all of which being optionally substituted with R^{150} ;
- e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, or heterocycle being optionally substituted with R^{150} ;
- f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;
- g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** or heterocycle being optionally substituted with R^{150} ;
- h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, or heterocycle being optionally substituted with R^{150} ;

- ₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
 or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H,
 5 (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;
 10 j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
 k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;
 15 l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰;
 wherein R¹⁵⁰ is selected from:
 - 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
 - 1 to 3 substituents selected from:
 25 a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;
 b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;
 30 d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are

covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

5 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;

10 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

15 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

20 **h)** NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl optionally substituted with R¹⁶⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-

cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰; and

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SR¹⁶¹, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both R¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, **Q** is a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)-**Het**,

all of which being optionally substituted with:

- 1 to 4 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 4 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is

- independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 5 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 10 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 15 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 20 h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl optionally substituted with R¹⁵⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆)alkyl or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;
- 25 i) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 30 j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;

-7)cycloalkyl , aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, said $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ and $(\text{C}_{1-6}\text{alkyl})\text{Het}$ being optionally substituted with R^{150} ;

k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$, $(\text{C}_{1-6}\text{alkyl})\text{Het}$ and heterocycle being optionally substituted with R^{150} ;

l) aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, all of which being optionally substituted with R^{150} , wherein R^{150} is preferably selected from:

- 1 to 3 substituents selected from: halogen, NO_2 , cyano or azido; or
- 1 to 3 substituents selected from:

a) $(\text{C}_{1-6})\text{alkyl}$ or haloalkyl, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{2-6})\text{alkenyl}$, $(\text{C}_{2-8})\text{alkynyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, all of which optionally substituted with R^{160} ;

b) OR^{104} wherein R^{104} is H, $(\text{C}_{1-6}\text{alkyl})$, $(\text{C}_{3-7})\text{cycloalkyl}$, or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, **Het**, said alkyl, cycloalkyl, aryl and **Het** being optionally substituted with R^{160} ;

c) OCOR^{105} wherein R^{105} is $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, said alkyl, cycloalkyl, aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ being optionally substituted with R^{160} ;

d) SR^{108} , $\text{SO}_2\text{N}(\text{R}^{108})_2$ or $\text{SO}_2\text{N}(\text{R}^{108})\text{C}(\text{O})\text{R}^{108}$ wherein each R^{108} is independently H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$ or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160} ;

e) $\text{NR}^{111}\text{R}^{112}$ wherein R^{111} is H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$ or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, and R^{112} is H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$ or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, COOR^{115} or $\text{SO}_2\text{R}^{115}$ wherein R^{115} is $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$, or heterocycle being optionally substituted

with R^{160} ;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, said (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het being optionally substituted with R^{160} ;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160} ;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6}) alkyl optionally substituted with R^{160} ; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or R^{124} is OH or $O(C_{1-6})$ alkyl, or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160} ;

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, said (C_{1-6}) alkyl and (C_{3-7}) cycloalkyl being optionally substituted with R^{160} ; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160} ;

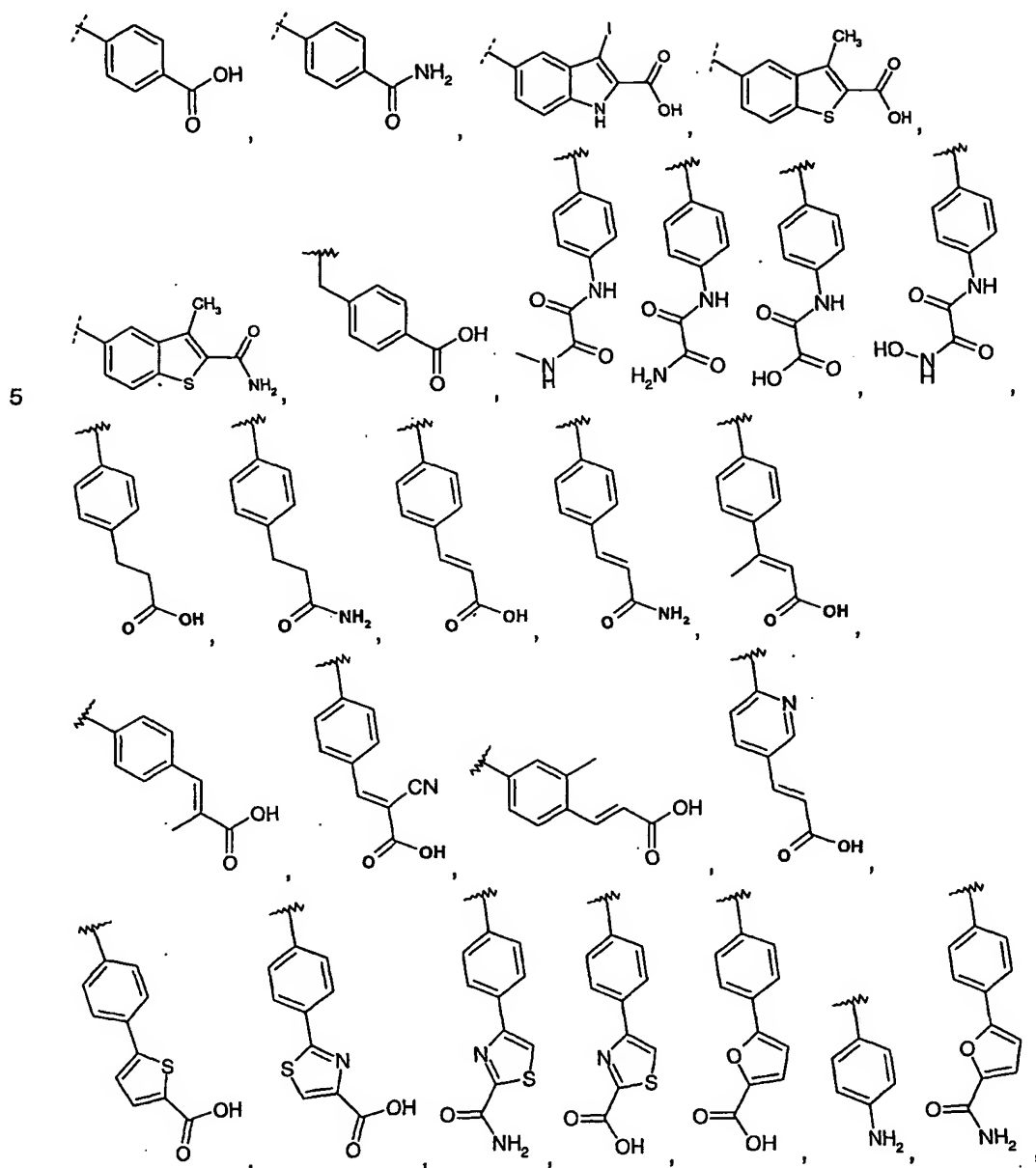
wherein R^{160} is defined as 1 or 2 substituents selected from:

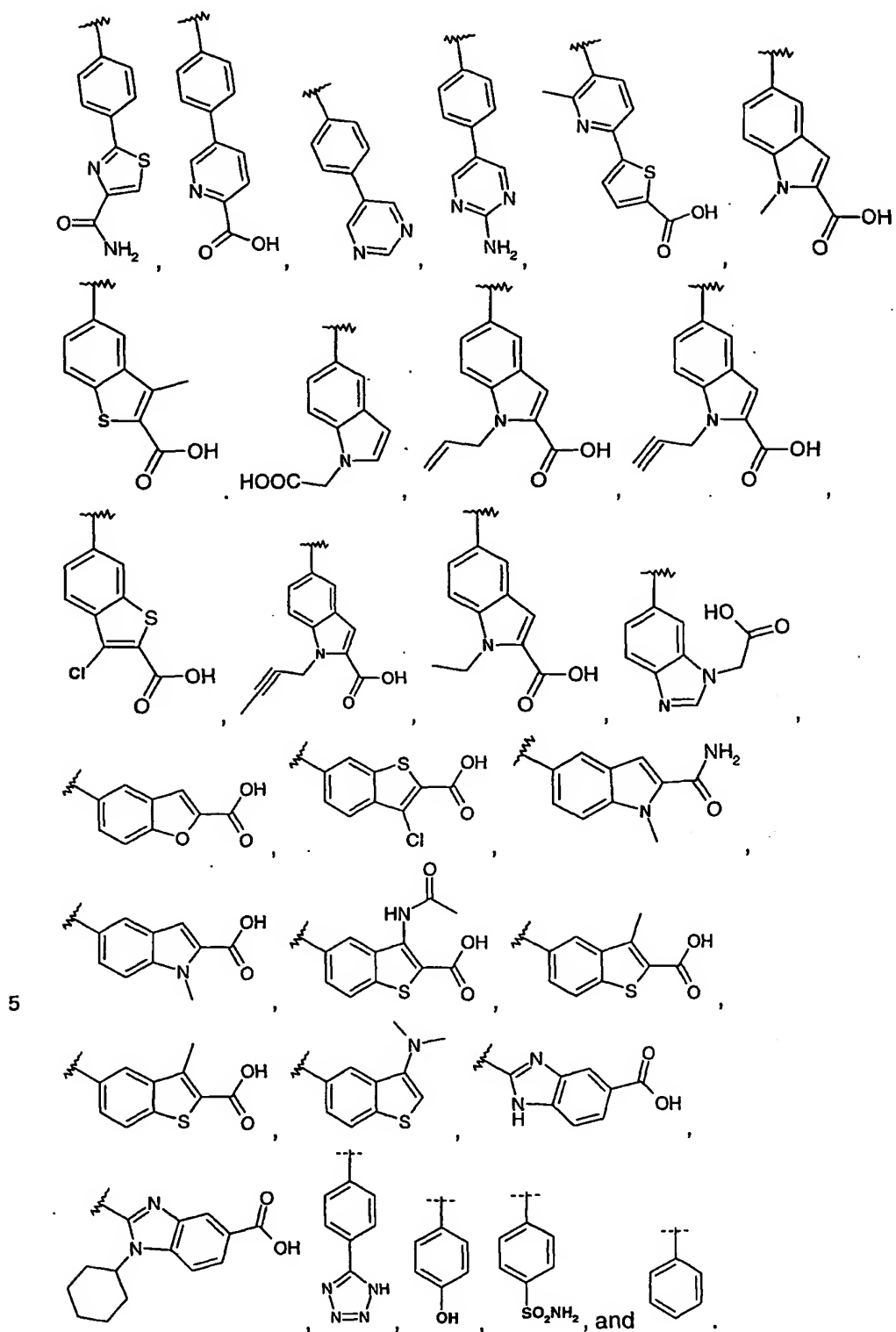
tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, SO_3H , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Most preferably, **Q** is a 6- or 10-membered aryl or **Het**, both being optionally substituted with:

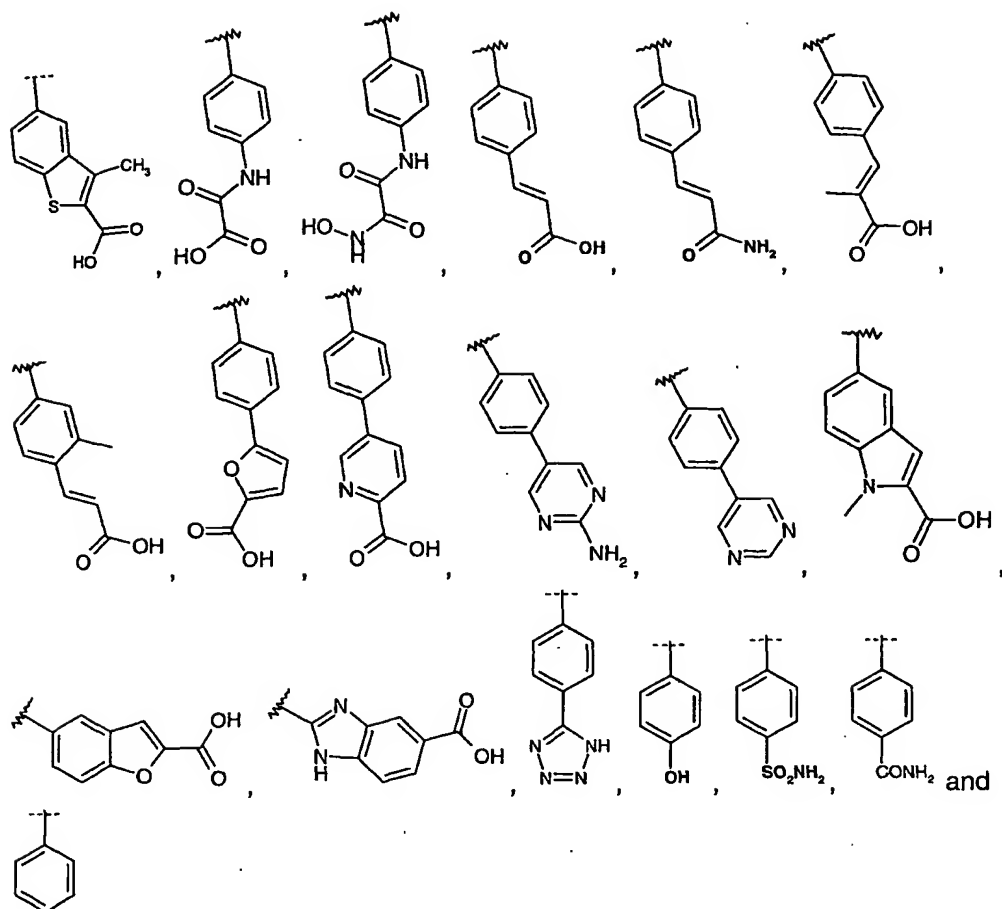
- 1 to 3 halogen, NO₂, cyano, azido; or
- 1 to 3 substituents selected from:
 - 5 **a)** first (C₁₋₆) alkyl or haloalkyl, first (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which are optionally substituted with R¹⁵⁰;
 - b)** OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl;
 - d)** SO₂NHR¹⁰⁸ wherein R¹⁰⁸ is H or (C₁₋₆)alkyl;
 - e)** NR¹¹¹R¹¹² wherein both R¹¹¹ and R¹¹² are independently H or (C₁₋₆)alkyl;
 - 10 **f)** NHCOR¹¹⁷ wherein R¹¹⁶ is H or (C₁₋₆)alkyl;
 - g)** NHCONR¹¹⁹R¹²⁰, wherein R¹¹⁹ and R¹²⁰ is each independently H or (C₁₋₆)alkyl;
 - h)** NHCOCOR¹²² wherein R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H or (C₁₋₆)alkyl;
 - 15 **j)** COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl;
 - k)** CONHR¹³⁰ wherein R¹³⁰ is H, (C₁₋₆)alkyl;
 - l)** 6- or 10-membered aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁵⁰; and
 - wherein, preferably, R¹⁵⁰ is selected from:
 - 20 - 1 to 3 halogens; or
 - 1 to 3 substituents selected from:
 - a)** first (C₁₋₆) alkyl or haloalkyl, first (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which are optionally substituted with tetrazole, OR¹⁰², COOR¹⁰², wherein R¹⁰² is H or (C₁₋₆)alkyl;
 - 25 **b)** OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl;
 - d)** SO₂NHR¹⁰⁸ wherein R¹⁰⁸ is H or (C₁₋₆)alkyl;
 - e)** NR¹¹¹R¹¹² wherein both R¹¹¹ and R¹¹² are independently H or (C₁₋₆)alkyl;
 - 30 **f)** NHCOR¹¹⁷ wherein R¹¹⁶ is H or (C₁₋₆)alkyl; and
 - h)** NHCOCOR¹²² wherein R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H or (C₁₋₆)alkyl);
 - j)** COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl; and
 - k)** CONHR¹³⁰ wherein R¹³⁰ is H, (C₁₋₆)alkyl.

More preferably **Q** is selected from:





Most preferably, Q is selected from:



5

Specific embodiments

Included within the scope of this invention are all compounds of formula I as presented in Tables 1 to 9.

10 Polymerase activity

The ability of the compounds of formula (I) to inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV can be demonstrated by any assay capable of measuring RNA dependent RNA polymerase activity. A suitable assay is described in the examples.

15

Specificity for RNA dependent RNA polymerase activity

To demonstrate that the compounds of the invention act by specific inhibition of HCV polymerase, the compounds may be tested for inhibitory activity in a DNA dependent RNA polymerase assay.

When a compound of formula (I), or one of its therapeutically acceptable salts, is employed as an antiviral agent, it is administered orally, topically or systemically to mammals, e.g. humans, rabbits or mice, in a vehicle comprising one or more
5 pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice.

For oral administration, the compound or a therapeutically acceptable salt thereof
10 can be formulated in unit dosage forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier.

For topical administration, the compound can be formulated in pharmaceutically
15 accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the active agent. Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of formula (I) is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with
20 pharmaceutically acceptable vehicles or carriers. For administration by injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

25 Suitable vehicles or carriers for the above noted formulations are described in pharmaceutical texts, e.g. in "Remington's The Science and Practice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds.,
30 Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum
35 effect under the circumstance is reached. In general, the compound of formula I is

most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound or a therapeutically acceptable salt is
5 administered in the range of 10 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 150 mg per kilogram.

For systemic administration, the compound of formula (I) is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the
10 aforementioned variations will occur. A dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

When the compositions of this invention comprise a combination of a compound of
15 formula I and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

When these compounds or their pharmaceutically acceptable salts are formulated
20 together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit HCV polymerase or to treat or prevent HCV virus infection. Such treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as α -, β -, or γ -interferons; other antiviral
25 agents such as ribavirin, amantadine; other inhibitors of HCV NS5B polymerase; inhibitors of other targets in the HCV life cycle, which include but not limited to, helicase, NS2/3 protease, NS3 protease, or internal ribosome entry site (IRES); or combinations thereof. The additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents
30 may be separately administered to a mammal as part of a multiple dosage form.

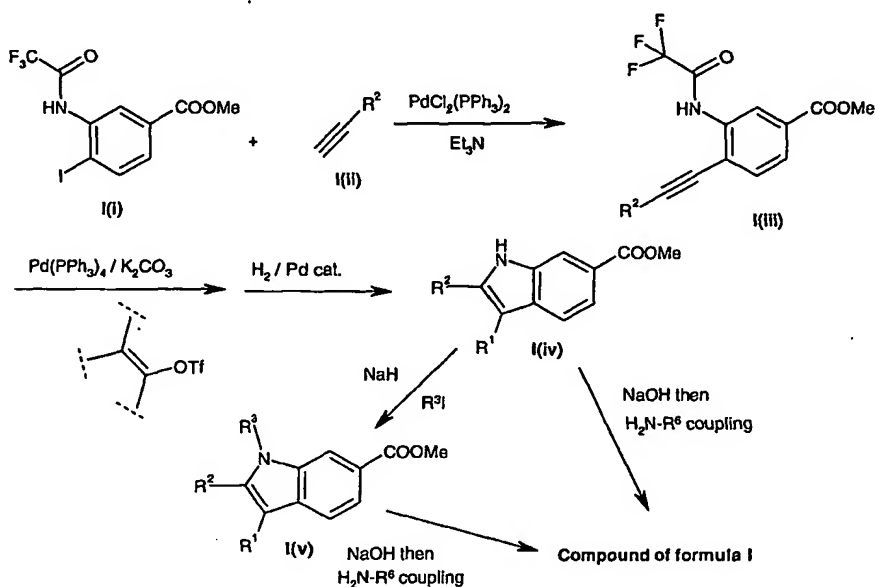
Methodology and Synthesis

Indole derivatives or analogs according to the present invention can be prepared from known monocyclic aromatic compounds by adapting known literature
35 sequences such as those described by J.W. Ellingboe et al. (*Tet. Lett.* 1997, 38,

7963) and S. Cacchi et al. (*Tet. Lett.* 1992, 33, 3915). Scheme 1, shown below wherein R^1 , R^2 , R^3 , R^6 , K, L, and M are as described herein illustrate how these procedures can be adapted to the synthesis of compounds of formula 1 of this invention.

5

Scheme 1



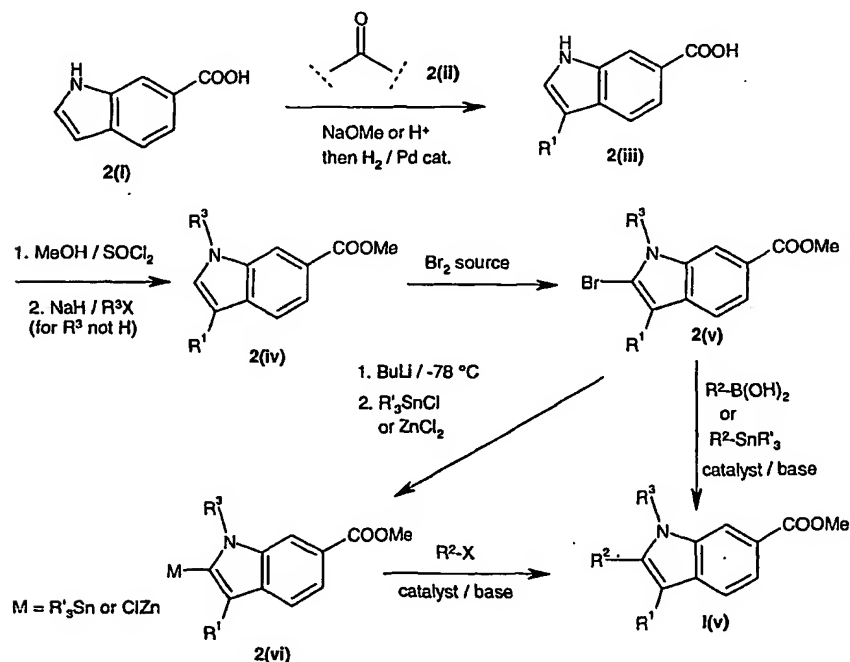
In carrying out the route illustrated in Scheme 1, a suitably protected form of 3-trifluoroacetamido-4-iodobenzoic acid **I(i)** is reacted with an alkyne **I(ii)** in the presence of a metal catalyst (e.g. a palladium metal complex such as $\text{PdCl}_2(\text{PPh}_3)_2$, Pd_2dba_3 , $\text{Pd}(\text{PPh}_3)_4$ and the like), a base (Et_3N , DIEA and the like or an inorganic basic salt including metal carbonates, fluorides and phosphates), and optionally in the presence of an additional phosphine ligand (triaryl or heteroarylphosphine, dppe, dppf, dppp and the like). Suitable solvents for this reaction include DMF, dioxane, THF, DME, toluene, MeCN, DMA and the like at temperatures ranging from 20 °C to 170 °C, or alternatively without solvent by heating the components together.

Alternatively, the cross-coupling reaction can be carried out on a suitably protected form of 3-amino-4-iodobenzoate and the amino group can be trifluoroacetylated in the subsequent step as described by J.W. Ellingboe et al. (*Tet. Lett.* 1997, 38, 7963). Reaction of the above diarylalkynes **I(iii)** with an enol triflate under cross-coupling conditions similar to those described above gives after hydrogenation of the double bond, indole derivatives **I(iv)**. Enol triflates are known and can be prepared from the corresponding ketones by following known literature methods (for example, cyclohexene triflate can be prepared from cyclohexanone, triflic anhydride and a

hindered organic base such as 2,6-di-*tert*-butyl-4-methylpyridine). The hydrogenation of the double bond originally present in R^1 can be carried out with hydrogen gas or a hydrogen donor (ammonium formate, formic acid and the like) in the presence of a metal catalyst (preferably Pd) in a suitable solvent (lower alkyl alcohols, THF etc.).

- Finally, following hydrolysis of the ester protecting group in **I(iv)**, the resulting 6-carboxyindole derivative **I(v)** is converted to compounds of formula **1** by coupling with the appropriate amine of formula H_2N-R^6 . Condensation of the 6-indolecarboxylic acid with amines H_2N-R^6 can be accomplished using standard amide bond forming reagents such as TBTU, HATU, BOP, BroP, EDAC, DCC, isobutyl chloroformate and the like, or by activation of the carboxyl group by conversion to the corresponding acid chloride prior to condensation with an amine. Any remaining protecting group is removed following this step to give compounds of formula **1**.
- Alternatively, compounds of formula **1** can be prepared by elaboration from a pre-existing indole core by following adaptations of literature procedures as described, for example, by P. Gharagozloo et al. (*Tetrahedron* **1996**, *52*, 10185) or K. Freter (*J. Org. Chem.* **1975**, *40*, 2525). Such a methodology is illustrated in Scheme 2:

Scheme 2



In carrying the route illustrated in Scheme 2, commercially available 6-indolecarboxylic acid **2(i)**, which can also be prepared according to the method of S. Kamiya et al. (*Chem. Pharm. Bull.* 1995, 43, 1692) is used as the starting material. The indole **2(i)** is reacted with a ketone **2(ii)** under basic or acidic aldol-type conditions. Suitable conditions to affect this condensation include strong bases such as alkali metal hydroxides, alkoxides and hydrides in solvents such as lower alkyl alcohols (MeOH, EtOH, *tert*BuOH etc.), THF, dioxane, DMF, DMSO, DMA and the like at reaction temperature ranging from -20 °C to 120 °C. Alternatively, the condensation can be carried out under acid conditions using organic or mineral acids or both. Appropriate conditions include mixtures of AcOH and aqueous phosphoric acid at temperatures ranging from 15°C to 120 °C.

Following protection of the carboxylic acid group in the form of an ester (usually lower alkyl) using known methods, the indole nitrogen can be alkylated with R³ if desired. Reaction conditions to alkylate the nitrogen of an indole derivative are well known to those skilled in the art and include the use of strong bases such as alkali metal hydrides, hydroxides, amides, alkoxides and alkylmetals, in the appropriate solvent (such as THF, dioxane, DME, DMF, MeCN, DMSO, alcohols and the like) at temperatures ranging from -78 °C to 140 °C. An electrophilic form of R³ is used for the alkylation of the indole anion. Such electrophilic species include iodides, bromides, chlorides and sulfonate esters (mesylates, tosylate, brosylate or triflate). Halogenation (usually bromination, but also iodination) of the 2-position of the indole **2(iv)** gives **2(v)**. Suitable halogenating agents include, for example, elemental bromine, *N*-bromosuccinimide, pyridine tribromide, dibromohydantoin and the corresponding iodo derivatives. Suitable solvents for this reaction are inert to reactive halogenating agents and include for example hydrocarbons, chlorinated hydrocarbons (DCM, CCl₄, CHCl₃), ethers (THF, DME, dioxane), acetic acid, ethyl acetate, IPA, and mixtures of these solvents. Reaction temperature ranges from -40 °C to 100 °C. A method of choice to carry out the bromination of indoles as shown in Scheme 2 was described by L. Chu (*Tet. Lett.* 1997, 38, 3871).

The 2-bromoindole derivatives **2(v)** can be converted directly to fully substituted key intermediates **1(v)** through a cross-coupling reaction with aryl or heteroaryl boronic acids, boronate esters or trialkylstannane derivatives. These boron or tin organometallic species are from commercial sources or can be prepared by standard literature procedures. Cross-coupling with organoboron reagents can be

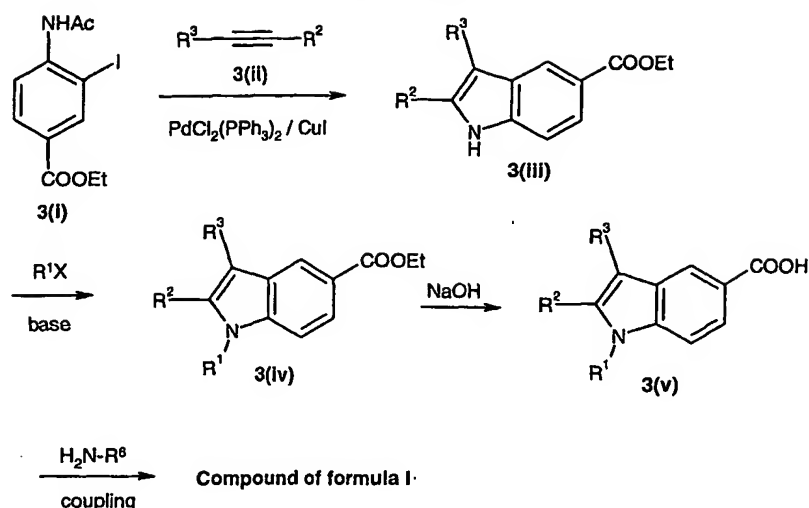
carried out by any variations of the Suzuki cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd⁰), triaryl or triheteroarylphosphine ligands, an additive such as an inorganic chloride (e.g. LiCl), and a base (usually an aqueous inorganic base such as sodium or potassium carbonate or phosphate). The reaction is usually carried out in an alcoholic solvent (EtOH), DME, toluene, THF and the like at temperatures ranging from 25 °C to 140 °C.

Cross-coupling with tin reagents can be carried out by any variations of the Stille cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd⁰), triaryl or triheteroaryl phosphine ligands, and an additive such as an inorganic chloride (e.g. LiCl) or iodide (e.g. CuI). Suitable solvents for this reaction include toluene, DMF, THF, DME and the like at temperatures ranging from 25 °C to 140 °C. Intermediate I(v) is then converted to compounds of formula 1 as described for Scheme 1.

Alternatively, the 2-bromoindole intermediate 2(v) can be trans-metallated to an organotin species (or organozinc) and used in Stille-type cross-coupling reactions under conditions described above. In this case, aromatic and heteroaromatic halides (chlorides, bromides, iodides) or triflates are used to introduce R². The conversion of 2-bromoindole derivatives 2(v) to the corresponding organotin species 2(vi) is carried out via initial low-temperature (usually -78 ° to -30 °C) halogen-metal exchange using an alkyllithium reagent (e.g. nBuLi or *tert*-BuLi) or using lithium metal. The transient 2-lithioindole species is then trapped with a trialkyltin halide (e.g. nBu₃SnCl or Me₃SnCl). Alternatively, the lithioindole intermediate can be trapped with zinc chloride to form the corresponding organozincate which can also undergo transition metal-catalyzed cross-coupling with aromatic and heteroaromatic halides or triflates as described, for example, by M. Rowley (*J. Med. Chem.* 2001, 44, 1603).

The present invention also encompasses compounds of formula 1 where the carboxylic group is in the 5-position of the indole system. The synthesis of such compounds is based on adaptation of literature procedures and is depicted in Scheme 3:

Scheme 3



In carrying out the synthetic route illustrated in Scheme 3, ethyl 4-acetamido-3-iodobenzoate **3(i)** undergoes metal catalyzed cross-coupling with an alkyne **3(ii)** to give a 2,3-disubstituted-5-indolecarboxylate **3(iii)** according to an adaptation of a procedure described by A. Bedeschi et al. (*Tet. Lett.* **1997**, 38, 2307). The indole derivative **3(iii)** is then alkylated on nitrogen with electrophilic R^1 groups (halides, sulfonate esters) under the action of a base such as alkali metal hydroxides, fluorides, hydrides, amides, alkyllithium, phosphabases and the like, to give **3(iv)**. Suitable solvents for this alkylation include DMF, DMA, DMSO, MeCN, THF, dioxane, DME and the like. Following saponification of the ester group with an alkaline solution, the resulting 5-indolecarboxylic acid derivative **3(v)** is coupled to $\text{H}_2\text{N-R}^6$ using an amide bond forming reagent as described previously (Scheme 1), to give compounds of formula I.

EXAMPLES

The present invention is illustrated in further detail by the following non-limiting examples. All reactions were performed in a nitrogen or argon atmosphere. Temperatures are given in degrees Celsius. Flash chromatography was performed on silica gel. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Mass spectral analyses were recorded using electrospray mass spectrometry. Abbreviations or symbols used herein include:

- DIEA: diisopropylethylamine;
DMAP: 4-(dimethylamino)pyridine;
DMSO: dimethylsulfoxide;
DMF: N,N-dimethylformamide;
- 5 Et: ethyl;
EtOAc: ethyl acetate;
Et₂O: diethyl ether;
HPLC: high performance liquid chromatography;
'Pr: isopropyl
- 10 Me: methyl;
MeOH: Methanol;
MeCN: acetonitrile;
Ph: phenyl;
TBE: tris-borate-EDTA;
- 15 TBTU: 2-(1*H*-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate;
TFA: trifluoroacetic acid;
TFAA: trifluoroacetic anhydride;
THF: tetrahydrofuran;
MS (ES): electrospray mass spectrometry;
- 20 PFU: plaque forming units;
DEPC: diethyl pyrocarbonate;
DTT: dithiothreitol
EDTA: ethylenediaminetetraacetate
HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium
hexafluorophosphate
- 25 BOP: benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
EDAC: see ECD
DCC: 1,3-Dicyclohexyl carbodiimide
HOBt: 1-Hydroxybenzotriazole
- 30 ES⁺: electro spray (positive ionization)
ES⁻: electro spray (negative ionization)
DCM: dichloromethane
TBME: *tert*-butylmethyl ether
TLC: thin layer chromatography
- 35 AcOH: acetic acid

EtOH: ethanol

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

BOC: *tert*-butoxycarbonyl

Cbz: carbobenzyloxy carbonyl

5 ⁱPrOH: isopropanol

NMP: N-methylpyrrolidone

EDC: 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

RNAasin: A ribonuclease inhibitor marketed by Promega Corporation

Tris: 2-amino-2-hydroxymethyl-1,3-propanediol

10 UMP: uridine 5'-monophosphate

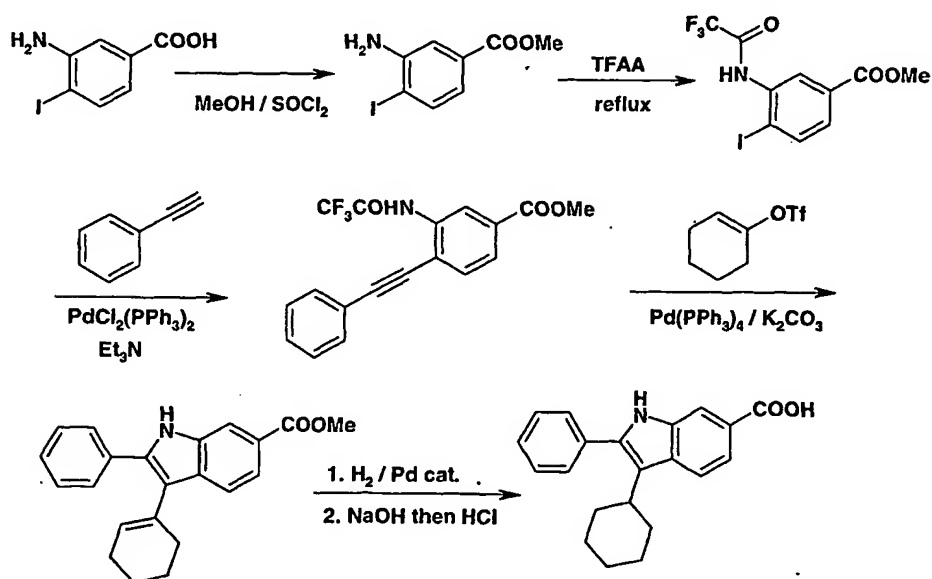
UTP: uridine 5'-triphosphate

IPA: isopropyl acetate

Examples 1-45 illustrate methods of synthesis of representative compounds of this

15 invention.

EXAMPLE 1



20

Methyl 3-amino-4-iodobenzoate:

3-Amino-4-iodobenzoic acid (13.35 g, 50.8 mmol) was added to MeOH (150mL) and SOCl₂ (4.8 mL, 65.8 mmol, 1.3 equivalent) was added. The mixture was refluxed for

3 h and then volatiles were removed under reduced pressure. The residue was co-evaporated three times with MeOH and dried in vacuo (15.23 g).

Methyl 3-trifluoroacetamido-4-iodobenzoate:

- 5 The aniline derivative from above (14.53 g, 52 mmol) was dissolved in DCM (200 mL) and TFAA (15 mL, 104 mmol) was added. The dark purple solution was refluxed overnight. Volatiles were removed under reduced pressure and the residue was passed through a short pad of silica gel using DCM as eluent. The desired product was obtained as a pink solid (13.81 g).

10

4-Phenylethynyl-3-(2,2,2-trifluoro-ethanoylamino)-benzoic acid methyl ester:

- The iodide from above (0.742 g, 2 mmol), phenylacetylene (0.37 mL, 3.9 mmol, 1.7 equivalent) and Et₃N (6 mL) were charged in a dry flask under argon. PdCl₂(PPh₃)₂ (0.241 g, 0.3 mmol) was added and the mixture was stirred at room temperature until judged complete by HPLC analysis (~5 h). The reaction mixture was concentrated to half volume under reduced pressure and diluted with water (80 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the organic extract washed with 5% HCl (100 mL), after (100 mL) and brine (40 mL). After drying over MgSO₄, the residue was purified by flash chromatography using 20% EtOAc – hexane as eluent to give the desired cross-coupled alkyne as a tan solid (0.442 g).

20

Methyl 3-(cyclohexenyl)-2-phenylindole 6-carboxylate:

- A flame-dried flask was charged with finely powdered anhydrous K₂CO₃ (0.153 g, 1.1 mmol) and the alkyne derivative from above (0.390 g, 1.1 mmol). Dry DMF (4 mL) was added and the suspension degassed with a stream of argon. The enol triflate derived from cyclohexanone, prepared following the procedure described by A.G. Martinez, M. Hanack et al. (*J. Heterocyclic Chem.* **1988**, *25*, 1237 or equivalent methods described in the literature, (0.802 g, 3.3 mmol, 3 equivalents) was added followed by Pd(PPh₃)₄ (0.086 g, 0.07 mmol) and the mixture was stirred for 8 h at room temperature. DMF was removed under vacuum and the residue purified by flash chromatography using DCM as eluent (0.260 g).

30

Methyl 3-cyclohexyl-2-phenylindole-6-carboxylate:

The material from above was hydrogenated (1 atm H₂ gas) over 20% Pd(OH)₂ in the usual manner, using MeOH as solvent. The desired cyclohexane indole was

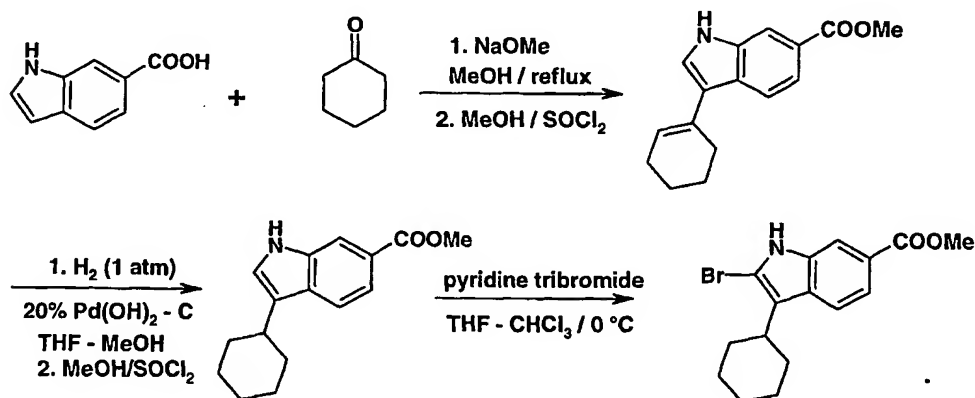
isolated after filtration of the catalyst.

3-Cyclohexyl-2-phenylindole-6-carboxylic acid:

The methyl ester from above (0.154 g, 0.15 mmol) was refluxed overnight in a mixture of MeOH (10 mL) and 2N NaOH (6 mL) until complete hydrolysis had occurred as shown by HPLC analysis. After cooling to room temperature, 2N HCl (5 mL) was added followed by AcOH to pH 7. MeOH was removed under reduced pressure, water (50 mL) was added and the product extracted with EtOAc. The extract was washed with water and brine, and dried (MgSO₄). Removal of volatiles under reduced pressure gave the title indole carboxylic acid as a light-orange solid (0.149 g).

Following the same procedure but using 2-ethynylpyridine instead of phenylacetylene, 3-cyclohexane-2-(2-pyridyl)indole-6-carboxylic acid was obtained.

EXAMPLE 2:



3-Cyclohexenyl-6-indole carboxylic acid:

A 12 L round-bottomed flask was equipped with a reflux condenser and a mechanical stirrer, and the system was purged with nitrogen gas. 6-Indole carboxylic acid (300.00 g, 1.86 mole, 3 equivalents) was charged into the flask, followed by MeOH (5.5 L). After stirring for 10 min at room temperature, cyclohexanone (579 mL, 5.58 mole) was added. Methanolic sodium methoxide (25% w/w, 2.6 L, 11.37 mole, 6.1 equivalents) was added in portions over 10 min. The mixture was then refluxed for 48 h. After cooling to room temperature, water (4

L) was added and methanol removed under reduced pressure. The residual aqueous phase was acidified to pH 1 with concentrated HCl (~1.2 L). The resulting yellowish precipitate was collected by filtration, washed with water and dried under vacuum at 50 °C. The desired cyclohexane derivative was obtained as a beige solid
5 (451.0g, 100% yield).

3-Cyclohexyl-6-indole carboxylic acid:

The unsaturated derivative from above was hydrogenated for 20 h under 55 psi hydrogen gas pressure over 20% Pd(OH)₂/C (10.25 g) using 1:1 THF – MeOH (2.5 L) as solvent. After filtration of the catalyst, volatiles were removed under reduced
10 pressure and the residue was triturated with hexane. The beige solid was collected by filtration, washed with hexane and dried under vacuum (356.4 g, 78% yield).

Methyl 3-cyclohexyl-6-indole carboxylate:

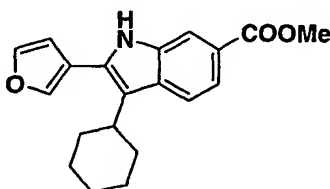
A 5 L three-necked flask was equipped with a reflux condenser and a mechanical
15 stirrer, and the system was purged with nitrogen gas. The indole carboxylic acid from above (300.00 g, 1.233 mole) was charged into the flask and suspended in MeOH (2 L). Thionyl chloride (5 mL, 0.0685 mole, 0.05 equivalent) was added dropwise and the mixture was refluxed for 48 h. Volatiles were removed under reduced pressure and the residue was triturated with hexane to give a beige solid
20 that was washed with hexane and dried under vacuum (279.6 g, 88% yield).

Methyl-2-bromo-3-cyclohexyl-6-indole carboxylate:

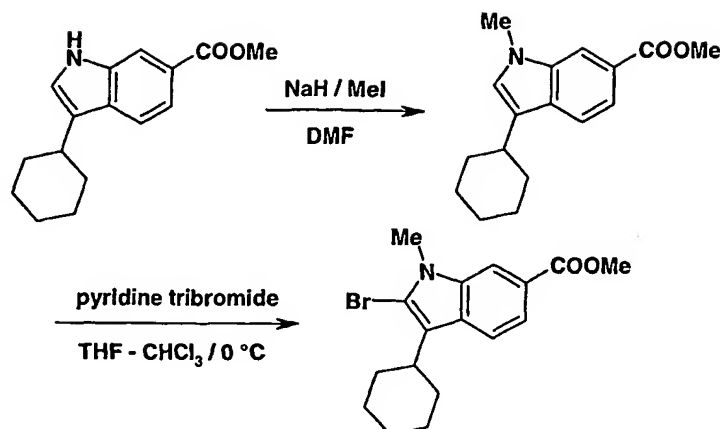
Adapting the procedure of L. Chu (*Tet. Lett.* 1997, 38, 3871) methyl 3-cyclohexyl-6-indole carboxylate (4.65 g, 18.07 mmol) was dissolved in a mixture of THF (80 mL) and CHCl₃ (80 mL). The solution was cooled in an ice bath and pyridinium bromide
25 perbromide (pyridine tribromide, 7.22 g, 22.6 mmol, 1.25 equivalent) was added. After stirring for 1.5 h at 0 °C, the reaction was judged complete by TLC. It was diluted with CHCl₃ (200 mL), washed with 1M NaHSO₃ (2 x 50 mL), saturated aqueous NaHCO₃ (2 x 50 mL) and brine (50 mL). After drying over Na₂SO₄, the
30 solvent was removed under reduced pressure and the residue crystallized from TBME – hexane. The desired 2-bromoindole derivative was collected by filtration, washed with hexane and dried (3.45 g). Evaporation of mother liquors gave a red solid that was purified by flash chromatography using 15% EtOAc in hexane yielding an additional 3.62 g of pure material. Total yield was 5.17 g (85% yield).

EXAMPLE 3:**General procedure for the Suzuki cross-coupling of aryl and heteroarylboronic acids with 2-bromoindole derivatives:**

Cross-coupling of aromatic/heteroaromatic boronic acid or ester derivatives with 2-bromoindoles such as the one described in example 2 can be performed using any variations of the standard metal-catalyzed Suzuki cross-coupling reaction as described in the literature and well known to those skilled in the art. The following example serves to illustrate such a process and is non-limiting.

3-Cyclohexyl-2-furan-3-yl-1H-indole-6-carboxylic acid methyl ester:

The 2-bromoindole of example 2 (8.92 g, 26.5 mmol), 3-furanboronic acid (B.P. Roques et al. *J. Heterocycl. Chem.* **1975**, *12*, 195; 4.45 g, 39.79 mmol, 1.5 equivalent) and LiCl (2.25 g, 53 mmol, 2 equivalents) were dissolved in a mixture of EtOH (100 mL) and toluene (100 mL). A 1M aqueous Na₂CO₃ solution (66 mL, 66 mmol) was added and the mixture was degassed with argon for 45 min. Pd(PPh₃)₄ (3.06 g, 2.65 mmol, 0.1 equivalent) was added and the mixture stirred overnight at 75-85 °C under argon. Volatiles were removed under reduced pressure and the residue re-dissolved in EtOAc (500 mL). The solution was washed with water, saturated NaHCO₃ (100 mL) and brine (100 mL). After drying over a mixture of MgSO₄ and decolorizing charcoal, the mixture was filtered and concentrated under reduced pressure. The residual oil was triturated with a mixture of TBME (20 mL) and hexane (40 mL), cooled in ice and the precipitated solid collected by filtration, washed with cold 25% TBME in hexane, and dried (3.09 g). The filtrate and washings from the above trituration were combined, concentrated and purified by flash chromatography using 10-25% EtOAc in hexane to give an additional 4.36 g of product. The total yield of the 2-(3-furyl)indole of example 3 was 8.25 g.

EXAMPLE 4:

5

Methyl 3-cyclohexyl-1-methyl-6-indole carboxylate:

Methyl 3-cyclohexyl-6-indole carboxylate from example 2 (150.00 g, 0.583 mole) was charged into a 3 L three-necked flask equipped with a mechanical stirrer and purged with nitrogen gas. DMF (1 L) was added and the solution was cooled in an ice-bath.

- 10 NaH (60% oil dispersion, 30.35 g, 0.759 mole, 1.3 equivalent) was added in small portions (15 min) and the mixture was stirred for 1 h in the cold. Iodomethane (54.5 mL, 0.876 mole, 1.5 equivalent) was added in small portions, maintaining an internal temperature between 5 – 10 °C. The reaction mixture was then stirred overnight at room temperature. The reaction was quenched by pouring into ice-water (3 L),
- 15 resulting in the formation of a cream-colored precipitate. The material was collected by filtration, washed with water and dried in vacuum at 45 °C (137.3 g, 86% yield).

Methyl 2-bromo-3-cyclohexyl-1-methyl-6-indole carboxylate:

The 1-methylindole derivative from above (136.40 g, 0.503 mole) was charged into a

20 5 L three-necked flask equipped with a mechanical stirrer and purged with nitrogen gas. CHCl₃ (750 mL) and THF (750 mL) were added and the solution was cooled to 0 °C. Pyridine tribromide (pyridinium bromide perbromide, 185.13 g, 0.579 mole, 1.15 equivalent) was added in small portions and the mixture was stirred for 1 h at 0 °C. The solvent was removed under reduced pressure at room temperature and the

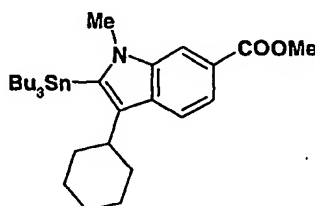
25 residue dissolved in EtOAc (3 L). The solution was washed with water and brine, dried (decolourising charcoal / MgSO₄) and concentrated under reduced pressure.

The residue was suspended in TBME and heated to 50 °C. The suspension was stored overnight in the refrigerator and the cream-coloured crystalline product was collected by filtration. It was washed with TBME and dried in vacuum (134.3 g, 76% yield).

5

EXAMPLE 5:

Cyclohexyl-methyl-tributylstannanyl-1H-indole-6-carboxylic acid methyl ester:

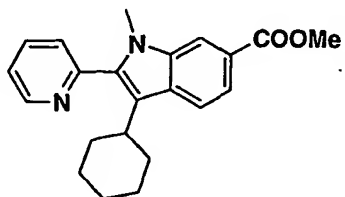


The bromoindole derivative of example 4 (2.70 g, 7.71 mmol) was dissolved in dry THF (40 mL) and the solution was cooled to -78°C under an argon atmosphere. A solution of $n\text{BuLi}$ in hexane (1.4 M, 6.90 mL, 9.64 mmol, 1.25 equivalent) was added dropwise over 15 min and stirring at low temperature was continued for 75 min. To the resulting suspension was added $n\text{Bu}_3\text{SnCl}$ (2.93 mL, 10.8 mmol, 1.4 equivalent) over 5 min. The suspension dissolved and the solution was stirred for 1 h at -78°C . The reaction mixture was warmed to room temperature and THF removed under reduced pressure. The residue was dissolved in TBME (150 mL), washed with 1:1 brine – water and dried over MgSO_4 . The material was purified by chromatography on silica gel that was previously deactivated by mixing with a solution of 5% Et_3N in hexane. The same solvent was used as eluent for the chromatography. The title stannane was isolated as a yellow oil (3.42 g, 79 % yield).

EXAMPLE 6:

General procedure for Stille cross-coupling of the 2-stannane indole of example 5 with aromatic/heteroaromatic halides:

Cross-coupling of aromatic/heteroaromatic halides or pseudohalides (preferably bromides, iodides and triflates) with the stannane derivative of example 5 can be performed using any variations of the standard metal-catalyzed Stille cross-coupling reaction as described in the literature. The following example serves to illustrate such a process.

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:

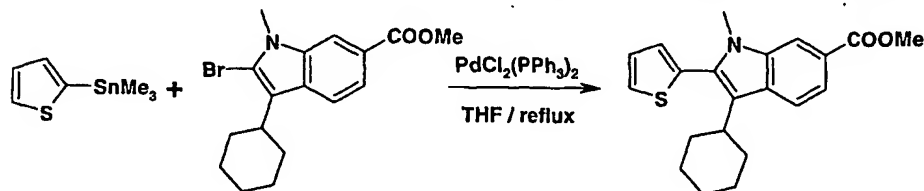
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The stannane derivative of example 5 (3.42 g, 6.1 mmol) was dissolved in DMF (10 mL) and CuI (0.116 g, 0.61 mmol, 0.1 equivalent), LiCl (0.517 g, 12.21 mmol, 2 equivalent), triphenylphosphine (0.320 g, 1.22 mmol, 0.2 equivalent) and 2-bromopyridine (0.757 mL, 7.94 mmol, 1.3 equivalent) were added. The solution was degassed with a stream of argon (30 min) and Pd(PPh₃)₄ (0.352 g, 0.31 mmol, 0.05 equivalent) was added. After purging with argon for an additional 10 min, the solution was heated and stirred at 100 °C overnight under argon. The DMF was then removed under vacuum and the residue dissolved in EtOAc (150 mL). The solution was washed with 1N NaOH (25 mL) and brine (25 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue purified by flash chromatography eluting with CHCl₃ then 5-10% EtOAc in CHCl₃ (1.516 g, 71% yield).

EXAMPLE 7:

General procedure for Stille cross-coupling of 2-bromoindoles with aryl or heteroaryl stannanes:

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:



The 2-bromoindole derivative of example 4 (0.150 g, 0.428 mmol) and 2-trimethylstannylthiophene (S.F. Thames et al. J. Organometal. Chem. 1972, 38, 29; 0.150 g, 0.61 mmol, 1.4 equivalent) were dissolved in dry THF (7 mL) in a sealed

tube, and the solution was degassed with a stream of argon for 30 min.

$\text{Pd}(\text{Cl})_2(\text{PPh}_3)_2$ (0.018 g, 0.026 mmol, 0.06 equivalent) was added and the tube sealed. The solution was heated to 80 °C for 40 h. The reaction mixture was cooled to room temperature, EtOAc (10 mL) was added and the suspension filtered. After
5 evaporation of the solvent, the residue was re-submitted to the reaction conditions for an additional 20 h, with fresh 2-stannylthiophene (0.150 g, 0.61 mmol) and catalyst (0.020 g). After cooling to room temperature and filtration of solids, the solvent was evaporated and the residue purified by flash chromatography using 15-100% CHCl_3 in hexane as eluent (0.133 g, 88% yield).

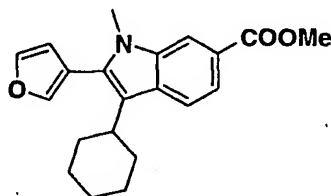
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The same procedure can be used to couple stannane derivatives to the 2-bromoindole of Example 2.

EXAMPLE 8:

15 **General procedure for the N-alkylation of 2-aryl and 2-heteroaryl-6-indole carboxylates:**

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid methyl ester:



NaH (60% oil dispersion, 0.186 g, 4.64 mmol, 1.5 equivalent) was washed with
20 hexane (20 mL) to remove the oil and then re-suspended in DMF (5 mL). After cooling to 0 °C in an ice bath, the indole derivative of example 3 (1.000 g, 3.09 mmol) was added dropwise as a solution in DMF (3 mL + 2 mL rinse). After stirring for 15 min, iodomethane (0.385 mL, 6.18 mmol, 2 equivalents) was added in one portion and the mixture was stirred for 2 h in the cold and an additional 2 h at room
25 temperature. The reaction was then quenched by addition of 1N HCl (1 mL) and diluted with TBME (100 mL). The solution was washed with 1N HCl (25 mL) and dried (MgSO_4). After removal of volatiles under reduced pressure, the residue was purified by flash chromatography using 5-10% EtOAc in hexane as eluent to give the title compound as a white solid (0.903 g, 86% yield).

30 Other N-alkylindole derivatives within the scope of this invention could be prepared from the appropriate electrophiles (e.g. EtI, iPrI, iBuI, BnBr) using a similar

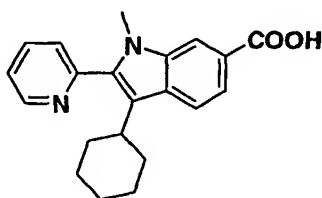
procedure.

EXAMPLE 9:

General procedure for the saponification of 6-Indolecarboxylates to the
5 corresponding free carboxylic acids:

This procedure applies to both indole and *N*-methylindole carboxylates.

3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid:



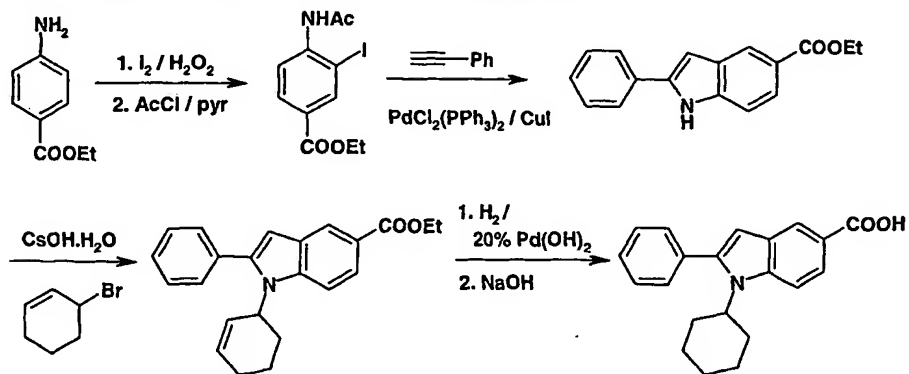
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The 6-indole carboxylate of example 6 (1.517 g, 4.35 mmol) was dissolved in DMSO (8 mL) and 5N NaOH (4.4 mL) was added. The mixture was stirred at 50 °C for 30 min. The solution was then cooled to room temperature and added dropwise to water (15 mL). Insoluble black impurities were removed by filtration and AcOH (2 mL) was added dropwise to the filtrate. The white precipitate that formed was collected by filtration, washed with water and dried (1.37 g, 94% yield).

15

EXAMPLE 10:

1-Cyclohexyl-2-phenyl-1H-indole-5-carboxylic acid:



20

Ethyl 4-amino-3-iodobenzoate:

Ethyl 4-aminobenzoate (15.00 g, 91 mmol) and iodine (11.80 g, 46.5 mmol) were mixed with water (80 mL) and chlorobenzene (4.60 g, 41 mmol). The mixture was stirred while the temperature was gradually raised to 90 °C over 30 min. Hydrogen peroxide (30%, 50 mL) was added over 10 h at 90 °C. After stirring at that
5 temperature for an additional 6 h, the mixture was cooled and the solution decanted from the residual solids. The solids were dissolved in DCM and the solution washed successively with sodium thiosulfate and brine. After drying (MgSO₄), the solvent was removed under reduced pressure and the resulting brown solid was triturated with hexane to remove di-iodinated by-products. The desired compound was
10 obtained as a brown solid (22.85 g, 86% yield).

Ethyl 4-acetamido-3-iodobenzoate:

The aniline from above (1.00 g, 3.44 mmol) was dissolved in pyridine (5 mL) and the solution was cooled in ice. AcCl (0.32 mL, 4.47 mmol, 1.3 equivalent) was added
15 dropwise and the mixture was stirred for 1 h at 0 °C and 2 h at room temperature. The reaction mixture was then diluted with 1 N HCl and the product was extracted with TBME (100 mL). The organic phase was washed with 1N HCl (50 mL), dried (MgSO₄) and concentrated to give the desired material as a tan-colored solid (1.121 g, 97% yield).

20

Ethyl 2-phenyl-indole-5-carboxylate:

Following the procedure of A. Bedeschi et al. (*Tet. Lett.* **1997**, *38*, 2307), the acetanilide derivative from above (0.900 g, 2.7 mmol) was reacted with phenylacetylene (0.385 mL, 3.5 mmol, 1.3 equivalent) in the presence of
25 PdCl₂(PPh₃)₂ (10 mole %) and CuI (10 mole %) in a mixture of dioxane (5 mL) and tetramethylguanidine (5 mL). The desired 2-phenylindole (0.589 g, 82% yield) was isolated as a yellow solid after flash chromatography with 15% EtOAc in hexane.

1-Cyclohex-1-enyl-2-phenyl-1H-indole-5-carboxylic acid ethyl ester:

The 2-phenylindole derivative from above (0.265 g, 1.0 mmol) was dissolved in DMF
30 (2 mL) and cesium hydroxide monohydrate (0.208 g, 1.2 mmol, 1.2 equivalent) was added. The solution was cooled in an ice bath and 3-bromocyclohexene (0.193 g, 1.2 mmol, 1.2 equivalent) was added dropwise (5 min) as a solution in DMF (1 mL). The mixture was stirred for 30 min at 0 °C. The reaction was diluted with water (25 mL), extracted with Et₂O (2 x 50 mL) and the extract dried over MgSO₄. The solvent

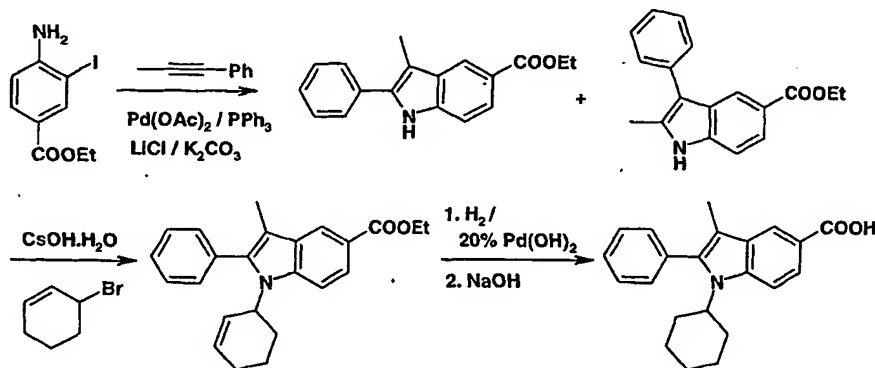
was evaporated under reduced pressure to give a white foam (0.095 g) that was used without purification in the next step.

1-Cyclohexyl-2-phenyl-1H-indole-5-carboxylic acid:

- The crude indole from above was hydrogenated in the usual way (1 atm H₂ gas) in EtOH over 20% Pd(OH)₂ on carbon for 20 h at room temperature. After filtration of the catalyst, the EtOH was removed under reduced pressure.
- The residue was dissolved in a mixture of MeOH (1 mL) and DMSO (1 mL) and 5N NaOH (0.5 mL) was added. The mixture was stirred overnight at 50 °C. The reaction mixture was cooled and water (10 mL) was added. After acidification with 1N HCl, the product was extracted into Et₂O (70 mL) and the solution dried (Na₂SO₄). Evaporation of the solvent gave a green residue consisting of a 2:1 mixture (85 mg) of the desired 1-cyclohexyl-2-phenylindole-5-carboxylic acid and 1,3-dicyclohexyl-2-phenylindole-5-carboxylic acid.

EXAMPLE 11:

1-Cyclohexyl-3-methyl-2-phenyl-1H-indole-5-carboxylic acid:



Ethyl 2-phenyl-3-methyl-indole-5-carboxylate:

- Adapting the procedure of H.-C. Zhang (*Tet. Lett.* **1997**, *38*, 2439) ethyl 4-amino-3-iodobenzoate (from example 10, 0.500 g, 1.72 mmol) was dissolved in DMF (5 mL) and LiCl (0.073 g, 1.72 mmol, 1 equivalent), PPh₃ (0.090 g, 0.34 mmol, 0.2 equivalent), K₂CO₃ (1.188 g, 8.6 mmol, 5 equivalents) and phenylpropyne (0.645 mL, 5.76 mmol, 3 equivalents) were added. The solution was degassed by purging with argon for 1 h and palladium acetate (0.039 g, 0.17 mmol, 0.1 equivalent) was added.
- The mixture was stirred at 80 °C under argon for 20 h. The reaction mixture was

diluted with water (25 mL) and extracted with EtOAc (50 mL). The extract was washed with brine (3 x 25 mL) and dried (MgSO₄). Concentration under reduced pressure and purification by flash chromatography with 10-15% EtOAc – hexane gave the desired 2-phenyl-3-methyl indole (0.275 g, least polar component) and the
5 3-phenyl-2-methyl isomer (0.109 g, more polar component).

Ethyl 1-(3-cyclohexenyl)-3-methyl-2-phenylindole-5-carboxylate:

The less polar isomer from above (0.264 g, 0.95 mmol) was dissolved in DMSO (2 mL) and cesium hydroxide monohydrate (0.191 g, 1.14 mmol, 1.2 equivalent) was
10 added followed by 3-bromocyclohexene (0.183 g, 1.14 mmol, 1.2 equivalent in 0.7 mL of DMSO). The mixture was stirred at room temperature for 30 min. Additional CsOH monohydrate (0.400 g, 2.4 equivalents) and 3-bromocyclohexene (0.400 g, 2.4 equivalents) were added and stirring continued for an additional 30 min. Similar amounts of the two reagents were again added and after another 30 min of stirring at
15 room temperature, the reaction was diluted with 1N HCl (6 mL) and water (20 mL). The product was extracted with TBME (100 mL), dried (MgSO₄) and after concentration under reduced pressure, the residue was purified by flash chromatography using 5-10% EtOAc in hexane as eluent. The desired *N*-alkylated indole was obtained (0.130 g).

20

Ethyl 1-cyclohexyl-3-methyl-2-phenylindole-5-carboxylate:

The unsaturated product from above was hydrogenated (1 atm H₂ gas) in the usual way over 20% Pd(OH)₂ in EtOH at room temperature for 3 h.

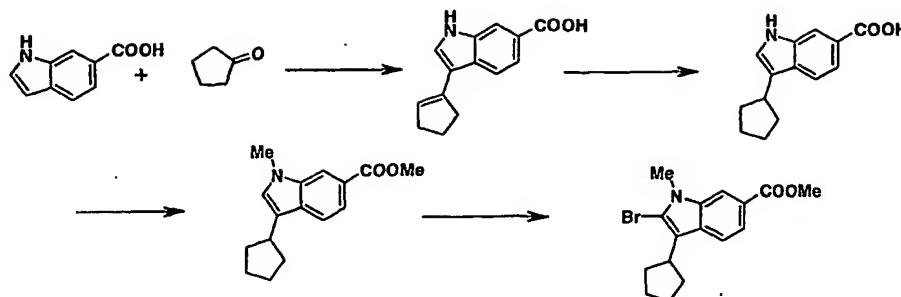
1-Cyclohexyl-3-methyl-2-phenyl-1H-indole-5-carboxylic acid:

25 The hydrogenated material from above was dissolved in a mixture of DMSO (2 mL) and MeOH (2 mL). 5N NaOH (0.5 mL) was added and the mixture was stirred overnight at 60 °C. After dilution with water (40 mL), the product aqueous phase was washed with a 1:1 mixture of Et₂O – hexane (50 mL) and then acidified with 1N HCl to pH 1. The liberated free acid was extracted with diethyl ether (2 x 50 mL) and
30 the extract dried over Na₂SO₄. Removal of the solvent under reduced pressure gave the desired indole as a light brown solid (0.074 g).

EXAMPLE 12:

2-Bromo-3-cyclopentyl-1-methyl-1H-indole-6-carboxylic acid methyl ester:

105



A 3 L three-necked flask equipped with a mechanical stirrer was charged with indole 6-carboxylic acid (220 g, 1.365 mole) and KOH pellets (764.45 g, 13.65 mole, 10 equivalents). Water (660 mL) and MeOH (660 mL) were added and the mixture
 5 heated to 75 °C. Cyclopentanone (603.7 mL, 6.825 mole, 5 equivalents) was added dropwise over 18 h using a pump. The reaction mixture was heated for an additional 3 h (after which the reaction was judged complete by HPLC) and cooled to 0 °C for 1 h. The precipitated potassium salt is collected by filtration, and washed with TBME (2 X 500 mL) to remove cyclopentanone self-condensation products. The brown
 10 solid was re-dissolved in water (2.5 L) and the solution washed with TBME (2 X 1 L). Following acidification to pH 3 with conc. HCl (425 mL), the beige precipitate was collected by filtration, washed with water (2 X 1 L) and dried under vacuum at 70 °C. The crude product weighed 275.9 g (88.9 % mass recovery) and had an homogeneity of 85% (HPLC).

15 The crude product from above (159.56 g, 0.70 mole) was dissolved in MeOH (750 mL) and 20% Pd(OH)₂ on charcoal (8.00 g) was added. The mixture was hydrogenated in a Parr apparatus under 50 psi hydrogen gas for 18 h. After completion, the catalyst was removed by filtration through celite and the solvent
 20 removed under reduced pressure. The resulting brown solid was dried at 70 °C under vacuum for 12 h. The crude product (153.2 g) was obtained as a brown solid and was 77% homogeneous by HPLC.

The crude 3-cyclopentylindole-6-carboxylic acid (74.00 g, 0.323 mole) was charged
 25 in a 3 L three-necked flask equipped with a mechanical stirrer and a thermometer. The system was purged with nitrogen gas and anhydrous DMF (740 mL) was added. After dissolution on the starting material, anhydrous potassium carbonate (66.91 g, 0.484 mole, 1.5 equivalent) was added and the mixture stirred for 5 minutes. Iodomethane (50 mL, 0.807 mole, 2.5 equivalents) was added and the mixture

stirred for 5 h after which HPLC analysis of the reaction mixture indicated 97% conversion to the methyl ester.

The reaction mixture was cooled in an ice bath and sodium hydride (95%, oil-free, 10.10 g, 0.420 mole, 1.3 equivalent) was added in small portions over 3 min (exothermic: 8 °C to 30 °C internal temperature raise). After stirring for an additional 15 min, the cooling bath was removed and stirring continued for 1.5 h at room temperature after which no further progression was observed (HPLC). Additional NaH (1.55 g, 65 mmol, 0.2 equivalent) and iodomethane (1.0 mL, 16 mmol, 0.05 equivalent) were added and after stirring for 15 min, the reaction was judged complete by HPLC (96% N-methylated).

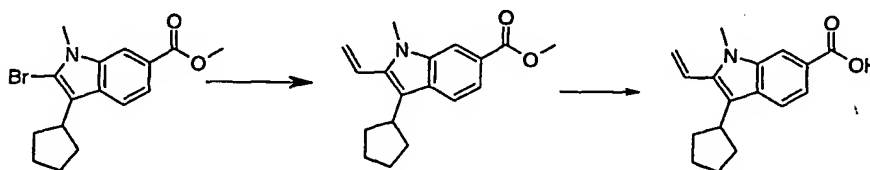
The reaction mixture was slowly (2 min) poured into water (4 L) with vigorous stirring and after 10 min, acidified to pH <2 with conc. HCl (85 mL). The mixture was stirred for 5 min to allow complete conversion of any remaining potassium carbonate and bicarbonate to the more soluble chloride. The pH was adjusted to ~7 with 4N NaOH (40 mL) and the mixture stirred overnight at room temperature. The precipitated material was collected by filtration, washed with water (600 mL) and dried at 60 °C under vacuum. The crude product (79% homogeneity by HPLC) was obtained as a brown solid (72.9 g).

The crude material from above is triturated with a minimal amount of MeOH to remove a series of minor impurities. The solid was then collected by filtration and dissolved in a minimal amount of hot EtOAc. After cooling to room temperature, hexane was added (5 X volume) and the mixture cooled in ice and filtered. The filtrate was then evaporated to dryness to give the desired product.

The *N*-methylindole from above (10.60 g, 41.2 mmol) was dissolved in isopropyl acetate (150 mL) and sodium acetate (5.07 g, 62 mmol, 1.5 equivalent) was added. The suspension was cooled in an ice bath and bromine (2.217 mL, 43.3 mmol, 1.05 equivalent) was added dropwise over 2 min. The pale amber suspension turned dark red (exotherm from 5 °C to 13 °C). It was stirred for 1 h at 0 °C. The reaction was completed by adding additional bromine (0.21 mL, 4.2 mmol, 0.10 equivalent) as shown by HPLC analysis. The reaction was then quenched by addition of 10% aqueous sodium sulfite solution (15 mL), followed by water (50 mL) and K₂CO₃ (10.6 g, 1.8 equivalent) to neutralize HBr. The organic layer was separated, washed with 10% aqueous sodium sulfite and aqueous K₂CO₃ and dried (MgSO₄). The solvent was removed under reduced pressure and the residue co-evaporated with TBME (75

mL) to give a beige solid that was dried under vacuum overnight (13.80 g). The crude material was triturated with boiling MeOH (80 mL) for 30 min, cooled in ice and the beige solid collected by filtration. The product was dried at 60 °C under vacuum (10.53 g, 76% recovery).

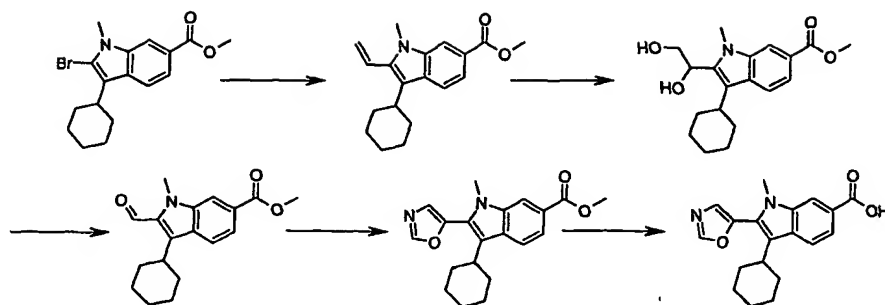
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EXAMPLE 13***3-Cyclopentyl-1-methyl-2-vinyl-1H-indole-6-carboxylic acid:***

- 10 To the 2-bromoindole derivative of example 12 (2.044 g, 6.08 mmol) in dry dioxane (20 mL) was added vinyltributyltin (1.954 mL, 6.69 mmol). The solution was degassed by bubbling nitrogen for 15 min. Then bis(triphenylphosphine) palladium (II) chloride (213.4 mg, 0.304 mmol) was added and the reaction mixture was heated at 100 °C overnight. The reaction mixture was diluted with ether and successively
- 15 washed with water and brine. After the usual treatment (MgSO₄, filtration and concentration) the residue was flash chromatographed (5 cm, 10% AcOEt-hexane) to afford the desired compound (1.32 g, 4.70 mmol, 77 % yield) as a white solid. To the ester from above (153 mg, 0.54 mmol) in a mixture of THF (2.8 mL) and methanol (1.4 mL) was added an aqueous solution of lithium hydroxide (226.6 mg,
- 20 5.40 mmol in 1.6 mL of water). The reaction mixture was stirred at 50 °C for 1.5 h and diluted with water. The aqueous layer was acidified with 1M aq. HCl and extracted three times with CH₂Cl₂. The combined organic layers were successively washed with water (2X) and brine. After the usual treatment (MgSO₄, filtration and concentration) the desired crude acid was isolated (150 mg).

25

EXAMPLE 14***3-Cyclohexyl-1-methyl-2-oxazol-5-yl-1H-indole-6-carboxylic acid:***



To the bromide of example 4 (1.00 g, 2.855 mmol) in dry dioxane (10 mL) was added vinyltributyltin (917.8 μ L, 3.141 mmol). The solution was degassed by bubbling
 5 nitrogen through for 15 min. Then bis(triphenylphosphine) palladium (II) chloride (101 mg, 0.144 mmol) was added and the solution was refluxed for 7 hrs. The reaction mixture was diluted with ether and successively washed with water and brine. After the usual treatment (MgSO_4 , filtration and concentration) the residue was flash chromatographed (5 cm, hexane to 2.5% AcOEt to 5% AcOEt to 10% AcOEt-
 10 hexane) to afford the desired compound (773 mg, 2.60 mmol, 91 % yield) as a pale yellow solid.

To the olefinic derivative from above (100 mg, 0.336 mmol) in a mixture of acetone (690 μ L), *tert*-butanol (690 μ L) and water (690 μ L) were successively added *N*-
 15 methylmorpholine *N*-oxide (NMMO; 48 mg, 0.410 mmol) and a 2.5 % solution of osmium tetroxide in *tert*-butanol (33 μ L). The reaction mixture was stirred at room temperature for three days and then concentrated. The residue was dissolved in EtOAc and successively washed with water (2X) and brine. After the usual treatment (MgSO_4 , filtration and concentration) the crude diol (117 mg) was isolated.

20 To the crude diol obtained above (ca. 0.336 mmol) in a mixture of THF (3.2 mL) and water (3.2 mL) at 0 $^{\circ}\text{C}$ was added sodium periodate (86.2 mg, 0.403 mmol). The cooling bath was then removed and the reaction mixture was stirred at room temperature for 1h 45 min, AcOEt was then added. The resulting solution was
 25 successively washed with 10% aq. citric acid, water, satd aq. NaHCO_3 , water (2X) and brine. After the usual treatment (MgSO_4 , filtration and concentration) the crude desired aldehyde was isolated (92 mg, 0.307 mmol, 91 % yield).

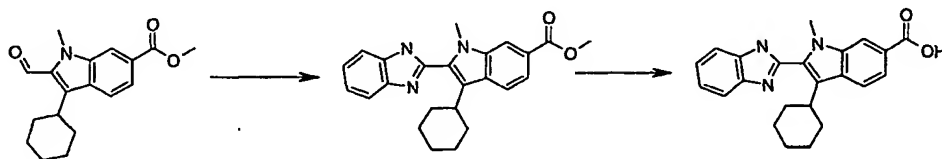
A mixture of the aldehyde from above (25.8 mg, 0.086 mmol), anhydrous potassium

carbonate (12.4 mg, 0.090 mmol) and Tosmic (17.57 mg, 0.090 mmol) in absolute MeOH (500 μ L) was refluxed for 2 h. AcOEt was then added and the mixture was successively washed with water (2X) and brine. After the usual treatment (MgSO₄, filtration and concentration) the crude desired oxazole was isolated (28 mg, 0.083 mmol, 96 % yield).

To the ester from above (28 mg, 0.083 mmol) in a mixture of THF (425 μ L), MeOH (210 μ L) and water (250 μ L) was added lithium hydroxide (34.8 mg, 0.830 mmol). The reaction mixture was stirred overnight at room temperature, then diluted with water and acidified with a 1N aq. HCl solution. The aqueous layer was extracted with dichloromethane (3X) and successively washed with water (2X) and brine. After the usual treatment (MgSO₄, filtration and concentration) the title crude acid was isolated (30 mg).

15 EXAMPLE 15

2-(1H-Benzimidazol-2-yl)-3-cyclohexyl-1-methyl-1H-indole-6-carboxylic acid:



To a mixture of the aldehyde from example 14 (28 mg, 0.094 mmol) and 1,2-diaminobenzene (10.9 mg, 0.101 mmol) in acetonitrile (500 μ L) and DMF (200 μ L) was added chloranil (24.8 mg, 0.101 mmol). The reaction mixture was stirred at room temperature for three days. AcOEt was added and the reaction mixture was successively washed with a 1N aq. NaOH solution (2X), water (4X) and brine. After the usual treatment (MgSO₄, filtration and concentration) the residue was flash chromatographed (1 cm, 30% AcOEt-hexane) to afford the desired benzimidazole ester derivative (11 mg, 0.028 mmol, 30 % yield).

25

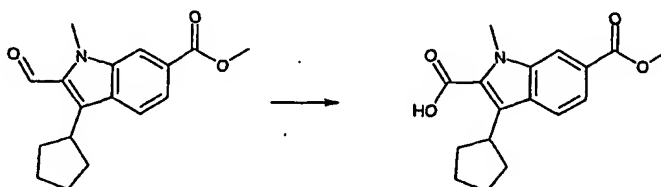
To the ester from above (11 mg, 0.028 mmol) in a mixture of THF (240 μ L), MeOH (120 μ L) and water (140 μ L) was added lithium hydroxide (11.7 mg, 0.280 mmol). The reaction mixture was stirred overnight at room temperature, then diluted with water and acidified with a 1N aq. HCl solution. The aqueous layer was extracted with dichloromethane (3X) and successively washed with water (2X) and brine. After the usual treatment (MgSO₄, filtration and concentration) the title crude acid was isolated

30

(9 mg, 0.0241 mmol, 86 % yield).

EXAMPLE 16

3-Cyclopentyl-1-methyl-1H-indole-2,6-dicarboxylic acid 6-methyl ester:

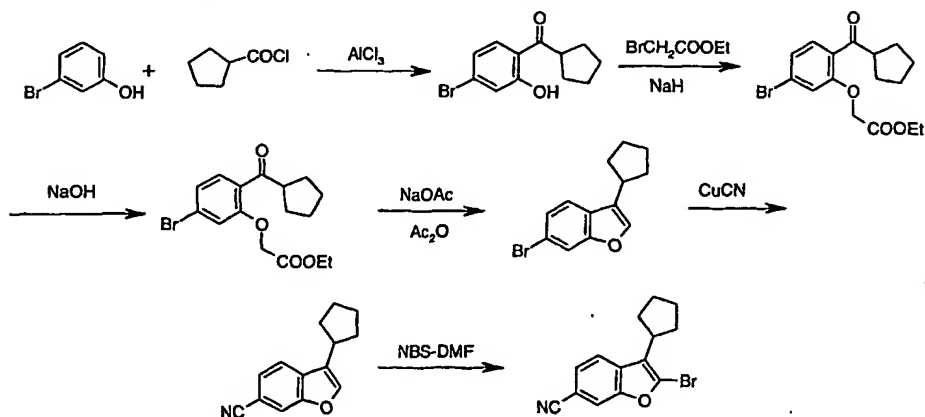


- 5 To the 3-cyclopentyl aldehyde prepared in a similar fashion to that described in example 15 (20 mg, 0.07 mmol) and 2-methyl-2-butene (541 μ L, 5.11 mmol) in tert-butanol (500 μ L) at 0 $^{\circ}$ C was added a freshly prepared solution of sodium chlorite (64.2 mg, 0.711 mmol) in phosphate buffer (98 mg of NaH_2PO_4 in 150 μ L of water).
- 10 The reaction mixture was stirred for 45 min. at room temperature then brine was added. The aqueous layer was extracted twice with EtOAc. The combined organic layer was successively washed with a 0.5 N aq. HCl solution and brine. After the usual treatment (MgSO_4 , filtration and concentration) 23.1 mg of the desired crude acid were isolated as a yellow solid.

15

EXAMPLE 17

2-Bromo-3-cyclopentyl-benzofuran-6-carbonitrile:



- 20 To a solution of 3-bromophenol (10 g, 57.8 mmol) in 1,2-dichloroethane (50 mL) was added AlCl_3 (11.5 g, 86.2 mmol), cautiously, in two equal portions at room temperature. Cyclopentanecarbonyl chloride (7.7 g, 58.1 mmol) was then added dropwise via syringe at room temperature. The reaction solution was then heated to

reflux under N₂ for a period of 2 hours. The reaction solution was cooled to room temperature and carefully poured into 100 ml of 1N HCl ice slush. After a few minutes of gentle stirring, the phases were separated and the aqueous phase was extracted with 1,2-dichloroethane. The organic phases were combined and washed with water and brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified on a pad of silica gel by hexanes. 17.2 g (78%) of the product was collected as a yellow liquid / low melting solid.

To a solution of the above phenol (12.2 g, 45.3 mmol) in 80 mL DMF at 0°C was added 60% NaH (2.67 g, 66.7 mmol). The ice bath was removed and the reaction solution was allowed to stir for 30 minutes. Ethyl Bromoacetate (11.4 g, 68.3 mmol) was then added dropwise via syringe. A mild exotherm (~40 °C) was observed, and the reaction solution was allowed to stir at room temperature for 1 hour. The reaction mixture was carefully poured into 150 ml of ice water, then acidified to pH 4-5 with 1N HCl. The reaction mixture was then extracted with EtOAc. The phases were separated and the organic fraction was washed with saturated NaHCO₃, water and brine, then dried over MgSO₄. The solvent was removed under reduced pressure. The crude material was taken to next step as is and treated as theoretical in yield.

16.1 g (45.3 mmol) of the above crude ester was combined with 61 mL of 1N NaOH and 137 mL of THF and stirred at room temperature overnight (additional 1N NaOH may be added if starting material persists.) Upon hydrolysis the THF was stripped off and the aqueous phase was extracted with EtOAc, which was discarded. The aqueous phase was then acidified to pH 2-3 with 1N HCl and extracted with EtOAc. The phases were separated and the organic phase was washed with water and brine, then dried over MgSO₄. The solvent was removed under reduced pressure. The crude material was taken to the next step as is and treated as theoretical in yield.

13.3 g (40.7 mmol) of the crude acid from above was dissolved in 200 mL Ac₂O. NaOAc (6.7 g, 81.7 mmol) was added and the resulting mixture was refluxed for 5 hours under N₂. The heat was removed and the reaction mixture was allowed to cool to room temperature. The reaction solution was then diluted with 100 mL toluene and neutralized with ice / 6N NaOH (STRONG EXOTHERMI). The phases were separated and the aqueous phase was extracted with EtOAc. The organic fractions were combined and washed with water and brine, then dried over MgSO₄.

The solvent was removed under reduced pressure and the residue was purified on a

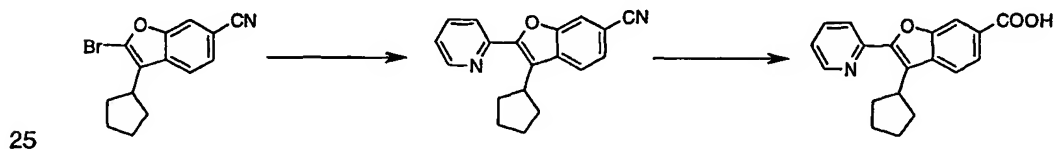
pad of silica gel by petroleum ether. 7.8 g (72%) of product was collected as a clear liquid / low melting solid.

The bromobenzofuran from above (29.6 g, 111.6 mmol) was dissolved in 60 mL DMF. CuCN (12.0 g, 134.0 mmol) was added and the resulting mixture was
5 refluxed under N₂ for 7 hours. The heat was removed and the reaction mixture was allowed to cool to room temperature. The reaction solution was poured into 300 mL of 5% aqueous NaCN, and 200 mL of EtOAc was added. The resulting solution was stirred gently until all solids went into solution. The layers were separated and the aqueous fraction was extracted with EtOAc. The organic fractions were combined
10 and washed with 5% aqueous NaCN, water and brine, then dried over MgSO₄. The solvent was removed under reduced pressure. The crude brown solid was cleaned up on a pad of silica gel by 10% EtOAc / Hexanes, and then purified by recrystallization in hexanes.

A solution of *N*-bromosuccinimide (5.340 g, 30 mmol) in DMF (20 mL) was added
15 dropwise to a solution of the above benzofuran derivative (2.00 g, 9.47 mmol) in DMF (20 mL). The mixture was stirred overnight at room temperature after which the bromination was judged complete (HPLC). The reaction mixture was diluted with EtOAc and washed successively with water (3 X) and brine. After drying (MgSO₄), the solvent was removed under reduced pressure and the residue purified by flash
20 chromatography using 3 % EtOAc in hexane to give the title 2-bromobenzofuran derivative as a white solid (1.45 g, 53 % yield).

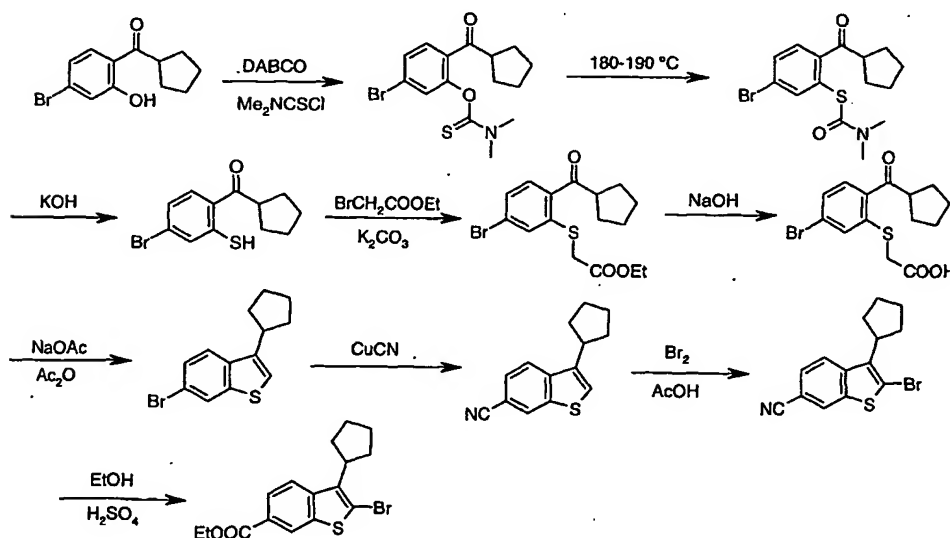
EXAMPLE 18

3-Cyclopentyl-2-pyridin-2-yl-benzofuran-6-carboxylic acid:



The 2-bromobenzofuran derivative of example 17 (0.850 g, 2.93 mmol), 2-tri(n-butyl)stannylpyridine (1.362 g, 3.7 mmol), triphenylphosphine (0.760 g, 2.90 mmol), lithium chloride (0.250 g, 5.9 mmol) and CuI (0.057 g, 0.3 mmol) were dissolved in DMF (30 mL) and the mixture was degassed by bubbling argon for 30 min. Tetrakis
30 (triphenylphosphine)palladium (0.208 g, 0.18 mmol) was added and the mixture stirred at 100 °C under an argon atmosphere. After 19 h, the reaction was cooled to room temperature, poured into water (70 mL) and extracted with TBME. The organic

phase was washed with water (2 X) and brine, dried (MgSO_4) and concentrated to give a residue that was purified by flash chromatography. The desired 2-(2-pyridyl)benzofuran derivative (0.536 g, 63 % yield) was obtained as a white solid. The nitrile from above (0.200 g, 0.694 mmol) was suspended in a mixture of conc. H_2SO_4 (5 mL), AcOH (4 mL) and water (2 mL). After refluxing for 1.5 h, TLC showed complete hydrolysis. The mixture was cooled in ice and the 10 N NaOH was added dropwise to pH 9. The aqueous layer was washed with dichloromethane and then acidified to pH 6 with 5 N HCl. The product was extracted with EtOAc, dried (MgSO_4) and solvents removed under reduced pressure. The desired carboxylic acid was obtained as a white solid.

EXAMPLE 19**2-Bromo-3-cyclopentyl-benzo[b]thiophene-6-carboxylic acid ethyl ester**

15

To a solution of 3-bromo-6-cyclopentanecarbonylphenol of Example 17 (5.194 g, 19.30 mmol) in DMF (58.0 mL) was added 1,4-diazabicyclo[2.2.2]octane (4.33 g, 38.60 mmol) and dimethylthiocarbamyl chloride (4.77 g, 38.6 mmol) at room temperature. The mixture was stirred at room temperature for 3 hr. The mixture was acidified with 1 N HCl to pH 3 and then extracted with EtOAc. The organic layers were combined and washed with brine and dried over MgSO_4 . The crude mixture was purified through a plug of silica gel with 3% EtOAc/hexanes to provide 6.976 g (100%) of the desired thiocarbamate as a colorless oil.

20

The neat O-3-bromo-6-cyclopentanecarbonyl N,N-dimethylthiocarbamate from

above (43.147 g, 121.1 mmol) was heated to internal temperature of 180-190°C for 5 hr. TLC (20% EtOAc/hexanes: R_f 0.6 (starting material), 0.5 (product)) was used to monitor the reaction progress. The crude material was used for the next reaction without further purification.

- 5 The crude *S*-3-bromo-6-cyclopentanecarbonyl *N,N*-dimethylthiocarbamate from above was dissolved in MeOH (600 mL), KOH (40.0 g, 714 mmol) was added and the mixture was heated to reflux for 1.5 h. The mixture was cooled to room temperature and the solvent was removed by rotary evaporation. The residue was dissolved in water and acidified by 6 N HCl to pH 3. It was extracted with EtOAc and
10 the crude product was purified by a silica gel chromatography with 1-5% EtOAc/hexanes. 31.3 g (91%) of the desired thiophenol derivative was obtained as a yellow oil.

- To a solution of the 3-bromo-6-cyclopentanecarbonylthiophenol from above (0.314 g, 1.105 mmol) in acetone (5.0 mL) was added K₂CO₃ (0.477 g, 3.45 mmol) followed by
15 addition of ethyl bromoacetate (0.221 g, 0.147 mL, 1.33 mmol). The mixture was stirred overnight. The reaction mixture was filtered through filter paper and the filtrate was concentrated. Purification by silica gel with 5% EtOAc/hexanes provided 0.334 g (82%) of the product as a colorless oil.

- The crude ester from above was dissolved in THF (12.0 mL), 1 N NaOH (5.0 mL)
20 was added at room temperature. The mixture was stirred at room temperature for 2-3 hr, or until TLC indicated complete reaction. The solvent was removed by rotary evaporation. Water was added and the mixture was acidified with 6 N HCl to pH 3 and extracted with EtOAc, washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was used without further
25 purification.

- To the crude acid from above was added acetic anhydride (16.0 mL), and then NaOAc (0.573 g) and the mixture was heated to reflux overnight. The mixture was cooled to room temperature and poured into a mixture of ice and toluene. 6 N NaOH was added until pH to about 7, and extracted with EtOAc, washed with brine and
30 dried over MgSO₄. The solvent was removed by rotary evaporation and the residue was purified by silica gel with hexanes to provide 0.795 g (80%) of 6-bromo-3-cyclopentyl benzothiophene as a colorless oil.

- A mixture of the 6-bromo-3-cyclopentylbenzothiophene from above (0.723 g, 2.57 mmol), and copper cyanide (0.272 g, 3.04 mmol) in DMF (1.4 mL) was heated to
35 reflux overnight. The mixture was cooled to room temperature and diluted with

EtOAc. 2 N NH_4OH was added and the mixture was stirred for 10 minutes and filtered through Celite. The aqueous layer was extracted with EtOAc. The organic layers were combined and washed with brine, dried over MgSO_4 , and the solvent was removed under reduced pressure. The product was used without further

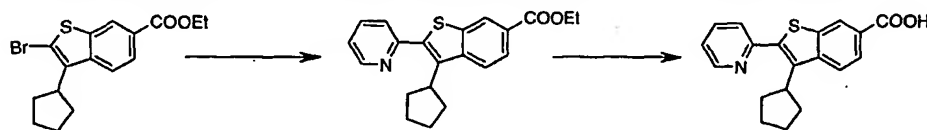
5 purification.

3-cyclopentyl-6-cyanobenzothiophene (17.65 g, 77.65 mmol) was dissolved in acetic acid (310 mL), bromine (49.64 g, 310.6 mmol) was added at room temperature. The mixture was stirred at room temperature overnight and HPLC was used to monitor the reaction progress. After the reaction was complete, toluene was added to the
10 reaction mixture to remove acetic acid (3 x 100 mL). The crude product was dried under reduced pressure and used without further purification.

The crude cyano derivative from above was added to ethanol (150 mL, denatured) and conc. H_2SO_4 (45 mL) and the mixture heated to reflux for 1-2 days. After completion (HPLC) the reaction mixture was cooled to room temperature and poured
15 into ice-water and extracted with dichloromethane (5 x 100 mL), the organic layers were combined and washed with 5% NaHCO_3 , and brine. The solvent was removed under reduced pressure and the residue was purified with silica gel by 1% EtOAc/hexanes. The collected fractions were concentrated and the residue was slurried in methanol. The solid was filtered and washed with ice-cold methanol to
20 provide 15.9 g (58%, two steps) of pure ethyl ester as a slight yellow solid.

EXAMPLE 20

3-Cyclopentyl-2-pyridin-2-yl-benzo[b]thiophene-6-carboxylic acid:



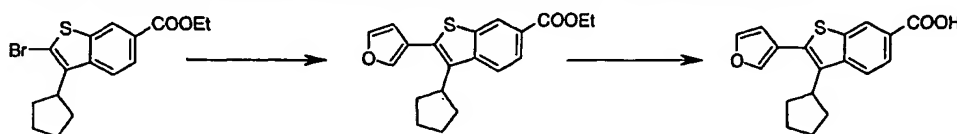
25 The 2-bromobenzothiophene of example 19 (0.354 g, 1.00 mmol), 2-tri(n-butyl)stannylpyridine (0.442 g, 1.2 mmol), triphenylphosphine (0.262 g, 1.00 mmol), lithium chloride (0.085 g, 2.0 mmol) and CuI (0.019 g, 0.1 mmol) were dissolved in DMF (10 mL) and the mixture was degassed by bubbling argon for 30 min. Tetrakis (triphenylphosphine)palladium (0.069 g, 0.06 mmol) was added and the mixture
30 stirred at 100 °C under an argon atmosphere. After 24 h, the reaction was cooled to room temperature, poured into water (70 mL) and extracted with TBME. The organic phase was washed with water (2 X) and brine, dried (MgSO_4) and concentrated to

give a residue that was purified by flash chromatography. The desired 2-(2-pyridyl)benzothiophene ester (0.197 g, 56 % yield) was obtained as a pale yellow waxy solid.

The ester from above was hydrolyzed in the usual manner using NaOH, to give the
 5 title acid that could be used directly or purified by HPLC and flash chromatography. The acid could be coupled to amine derivatives following the general procedure described in example 37.

EXAMPLE 21

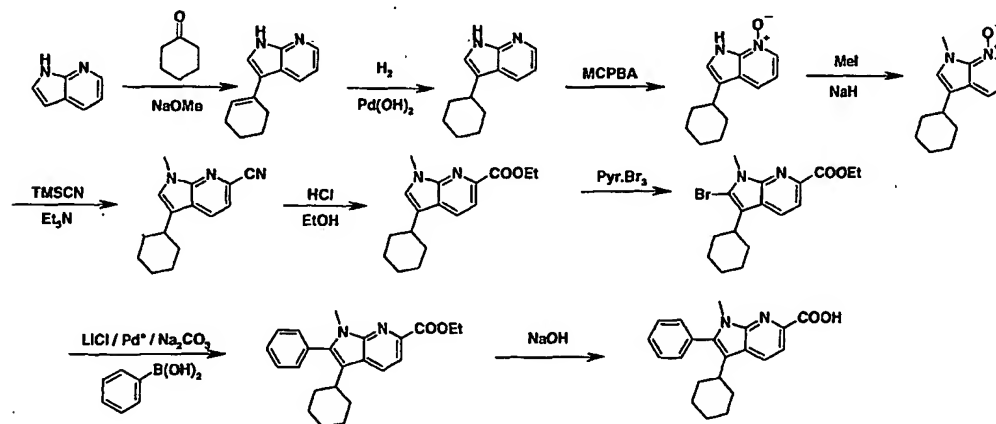
10 3-Cyclopentyl-2-furan-3-yl-benzo[b]thiophene-6-carboxylic acid:



The 2-bromobenzothiophene ester of example 19 was coupled to 3-furanboronic
 acid as described in example 3 to give the desired 2(3-furyl)benzothiophene ester in
 85 % yield. Saponification of the ethyl ester was carried out with NaOH at room
 15 temperature to give the title carboxylic acid derivative.

EXAMPLE 22

3-Cyclohexyl-1-methyl-2-phenyl-1H-pyrrolo[2,3,b]pyridine-6-carboxylic acid:



20

7-Azaindole (15.00 g, .127 mole) was dissolved in MeOH (330 mL) and sodium methoxide (25% w/w in MeOH, 172 mL, 0.753 mole) and cyclohexanone (52.86 mL, 0.51 mole) were added. The mixture was refluxed for 60 h and then concentrated under reduced pressure. After cooling in ice-water, the reaction mixture was

acidified to pH 8 with 3N HCl and the precipitated solid was collected by filtration. The product was washed with water, triturated with TBME-hexane and dried by azeotroping with toluene (19.8 g).

The material from above (15.00 g, 75.65 mmol) was dissolved in a mixture of EtOH (130 mL) and THF (30 mL) and 20% Pd(OH)₂ on carbon (1.30 g) was added. The mixture was hydrogenated under 1 atm of H₂ gas for 24 h, after which point additional catalyst (1.30 g) was added. After stirring under H₂ gas for an additional 16 h, the catalyst was removed by filtration and the solution evaporated under reduced pressure to give a residue that was triturated with TBME to give an amber solid (13.9 g).

The azaindole derivative from above (7.50 g, 37.45 mmol) was dissolved in DME (130 mL) and *meta*-chloroperbenzoic acid (12.943 g, 60.0 mmol) was added. After stirring for 2 h, volatiles were removed under reduced pressure and the residue suspended in water (100 mL). The mixture was basified to pH 10 by addition of saturated aqueous Na₂CO₃ solution under vigorous stirring. The solid was then collected by filtration, washed with water and a small amount of TBME, and dried (7.90 g).

The crude N-oxide from above (4.00 g, 18.49 mmol) was dissolved in DMF (350 mL) and NaH (60% dispersion, 1.52 g, 38 mmol) was added in small portions over 5 min. The mixture was stirred for 30 min and iodomethane (1.183 mL, 19 mmol) was added dropwise over 20 min to the suspension. After stirring for 3 h at room temperature, no more progress was measured by HPLC analysis. The reaction mixture was poured into water and extracted 3 times with EtOAc. The extract was washed with brine, dried (MgSO₄) and evaporated to give an amber solid (3.65 g, 60% homogeneity by NMR) that was used immediately without purification.

The crude product from above (0.80 g, 3.47 mmol) was dissolved in MeCN (10 mL). Triethylamine (1.13 mL, 8.1 mmol) was added followed by trimethylsilyl cyanide (2.13 mL, 16 mmol). The solution was then refluxed for 19 h. After cooling to room temperature, the reaction was quenched by slow addition of aqueous NaHCO₃ and the product extracted with EtOAc. The extract was washed with brine, dried (MgSO₄) and concentrated to a residue that was purified by flash chromatography on silica gel using 15% EtOAc-hexane (0.285 g).

The nitrile (0.300 g, 1.254 mmol) was suspended in EtOH (15 mL) and hydrogen chloride gas was bubbled through for 15 min to give a clear solution. The solution was then refluxed for 1.5 h until TLC showed complete conversion of starting

material. After cooling to room temperature, volatiles were removed under reduced pressure and the residue was dissolved in EtOAc. The solution was washed with brine, dried (MgSO_4) and concentrated. The residue was purified by flash chromatography on silica gel (15-20% EtOAc-hexane) to give the desired ethyl ester as a pale yellow gum (0.227 g).

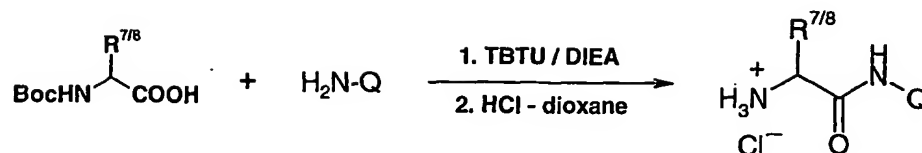
5 The ester from above (0.100 g, 0.35 mmol) was dissolved in THF (4 mL) and pyridinium hydrobromide perbromide (0.200 g, 0.532 mmol) was added. The mixture was stirred at 65 °C in a sealed vial for 16 h (>80% conversion). The solution was evaporated and the residue taken up into EtOAc. The solution was washed with
10 water and brine, dried (MgSO_4) and concentrated. The crude material was purified by flash chromatography on silica gel (15% EtOAc-hexane).

The bromide from above (0.100 g, 0.274 mmol), phenylboronic acid (0.049 g, 0.4 mmol) and lithium chloride (0.019 g, 0.45 mmol) were dissolved in a mixture of toluene (2 mL), EtOH (2 mL) and 1M Na_2CO_3 (0.43 mL). The mixture was degassed.
15 by passing argon gas through the solution for 30 min, and tetrakis(triphenylphosphine) palladium (0.035 g, 0.03 mmol) was added. The mixture was refluxed for 18 h after which point more catalyst (0.035 g, 0.03 mmol) was added. After refluxing for an additional 2 h, the EtOH was removed under reduced pressure. The residue was dissolved in EtOAc and the solution washed with 10% aqueous HCl and brine, and
20 dried (MgSO_4). Removal of volatiles under reduced pressure gave an orange gum that was purified by flash chromatography on silica gel using 20% EtOAc-hexane (0.105 g, crude).

The partially purified ester from above (0.100 g, 0.276 mmol) was dissolved in a mixture of THF (2 mL) and EtOH (2 mL). 1N NaOH (2.8 mL) was added and the
25 mixture stirred for 4 h at room temperature. Volatiles were removed under reduced pressure and the residue diluted with 10% aqueous HCl. The product was extracted with EtOAc (3 X), dried (MgSO_4), evaporated and purified by reversed-phase preparative HPLC to give the title compound.

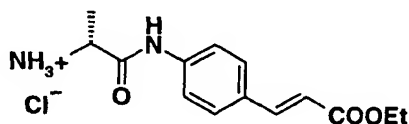
30 **EXAMPLE 23:**

General procedure for the preparation of aromatic amide derivatives from α -monosubstituted N-Boc-amino acids:



N-Boc protected α -monosubstituted amino acids were coupled to aromatic amine derivatives using standard amide bond coupling reagents. The *N*-Boc protecting group was then cleaved under acidic conditions and the appropriate amine derivatives were isolated as hydrochloride salts. The following procedure for coupling *N*-Boc-D-alanine to ethyl 4-aminocinnamate is representative:

(*R*)-1-[4-((*E*)-2-Ethoxycarbonyl-vinyl)-phenylcarbamoyl]-ethyl-ammonium chloride:

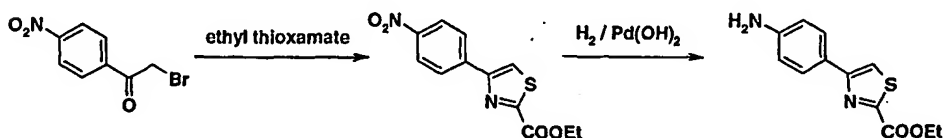


N-Boc-D-alanine (0.284 g, 1.5 mmol) was dissolved in DMSO (2 mL) and DIEA (1.04 mL, 6 mmol, 4 equivalents) was added. Ethyl 4-aminocinnamate (0.287 g, 1.5 mmol) was added followed by TBTU (0.578 g, 1.80 mmol) and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with EtOAc (75 mL) and the solution washed with water (40 mL), 1N NaOH (3 x 25 mL), 1M KHSO₄ (2 x 25 mL) and 5% NaHCO₃ (25 mL). The extract was dried (MgSO₄) and concentrated to give the desired *N*-Boc-protected anilide as a yellow solid (0.411 g). The material from above was stirred for 1 h with 4N HCl in dioxane (10 mL). Removal of volatiles under reduced pressure and trituration of the residue with TBME gave the title hydrochloride salt as a brown solid.

20

EXAMPLE 24:

4-(4-Amino-phenyl)-thiazole-2-carboxylic acid ethyl ester:



4'-Nitro-2-bromoacetophenone (6.100 g, 25 mmol) and ethyl thioxamate (3.460 g, 26 mmol) were dissolved in MeOH (20 mL) and the solution was refluxed for 1 h. After

25

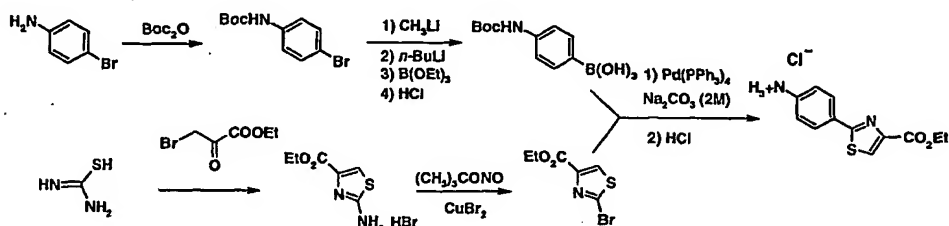
cooling to room temperature, the precipitated solid was collected by filtration, washed with cold MeOH and dried under vacuum (5.15 g, 75% yield).

A suspension of the nitroester from above (2.50 g, 8.98 mmol) and 20% Pd(OH)₂ on carbon (200 mg) in 2:1 EtOH – THF (60 mL) was stirred for 3 h under 1 atm of hydrogen gas. The suspension was filtered to remove the catalyst and volatiles removed under reduced pressure to give the title compound as a reddish foam (2.05 g, 92% yield).

EXAMPLE 25:

4-(4-Ethoxycarbonyl-thiazol-2-yl)-phenyl-ammonium chloride:

10



p-Bromoaniline (13.0 g, 76 mmol) and Boc₂O (19.8 g, 91 mmol) were dissolved in toluene (380 mL) and stirred at 70 °C for 15 h. The reaction mixture was cooled to RT, evaporated to dryness, re-dissolved in EtOAc and washed with 0.1M HCl and brine. The organic solution was dried over anhydrous MgSO₄, evaporated to dryness and purified by flash column chromatography, using 5% to 10% EtOAc in hexane as the eluent, to obtain the Boc-protected aniline (23 g). The Boc-protected bromoaniline (10.7 g, 39.2 mmol) was dissolved in anhydrous THF (75 mL) in a flask equipped with an overhead stirrer. The solution was cooled to 0 °C and MeLi (1.2 M in Et₂O, 33 mL, 39.2 mmol) was added drop wise while maintaining the internal temperature below 7 °C. The reaction mixture was stirred at 0 °C for 15 min and then cooled to –78 °C before *N*-BuLi (2.4 M in hexane, 17 mL, 39.2 mmol) was added drop wise, maintaining the internal temperature below –70 °C). The reaction mixture was stirred at –78 °C for 1h, B(OEt)₃ (17 mL, 98 mmol) was added drop wise (internal temperature < –65 °C) and stirring was continued for 45 min at –78 °C and at 0 °C for 1 h. The reaction mixture was then treated with 5% aqueous HCl (~100 mL, to pH ~1) for 15 min and NaCl(s) was added to saturate the aqueous layer. The aqueous layer was extracted with 0.5 M NaOH (4 x 100 mL) and the combined

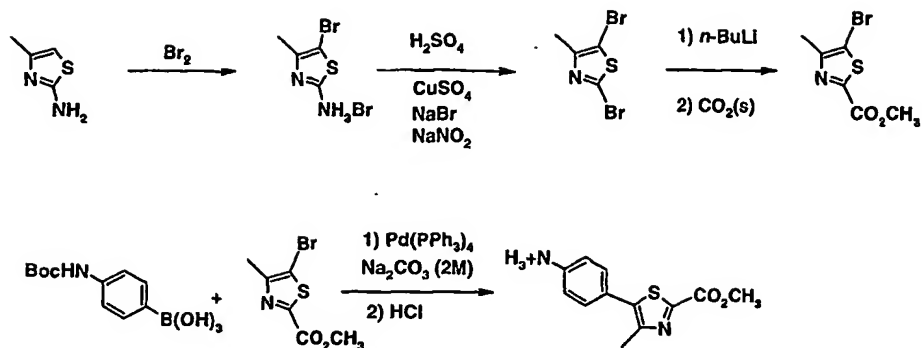
aqueous layers were acidified with 5% HCl (150 mL, to pH ~1) and extracted with Et₂O (3 x 200 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated to give the *N*-Boc carbamate of 4-aminophenylboronic acid as a solid (7.5 g).

- 5 Thiourea (7.60 g, 100 mmol) and ethyl bromopyruvate (12.6 mL, 100 mmol) were mixed and heated to 100 °C for 45 min. After cooling of the reaction mixture, the solid obtained was triturated with acetone, filtered and recrystallized from EtOH to obtain the desired aminothiazole product (10.6 g, 40 mmol). The aminothiazole was then added slowly (over a period of 20 min) to a solution of *t*-butylnitrite (6.2 g, 60
- 10 mmol) and CuBr₂ (10.7 g, 48 mmol) in MeCN (160 mL) at 0 °C. The reaction mixture was allowed to warm-up to RT and to stirred for 2.5 h. The mixture was then added to an aqueous HCl solution (20%) and extracted with Et₂O (2 x 400 mL). The organic layer was washed with aqueous HCl (10%), dried over anhydrous MgSO₄ and evaporated to dryness. The desired bromothiazole product was isolated in
- 15 ~85% yield (4.3 g) after flash column chromatography using 15% EtOAc in hexane as the eluent.

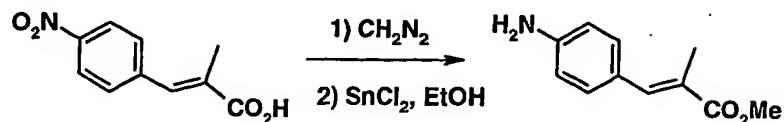
- To a de-gassed solution of the bromothiazole product (230 mg, 0.97 mmol), the boronic acid derivative from above (230 mg, 0.97 mmol) and aqueous Na₂CO₃ (2M, 3 mL) in DME (3mL), a catalytic amount of Pd(PPh₃)₄ (56 mg, 0.049 mmol) was
- 20 added and the reaction mixture was stirred at 80 °C under argon for 20 h. The reaction mixture was then cooled to RT, diluted with EtOAc and extracted with brine, aqueous NaHCO₃ (2 x) and brine. The organic layer was dried over anhydrous MgSO₄ and concentrated to dryness. The carbamate-ester product was isolated after flash column chromatography using 20% to 30% EtOAc in hexane: 180 mg.
- 25 The aniline hydrochloride was isolated after removal of the Boc protecting group with 4N HCl in dioxane for 30 min.

EXAMPLE 26:

4-(2-Methoxycarbonyl-4-methyl-thiazol-5-yl)-phenyl-ammonium chloride:

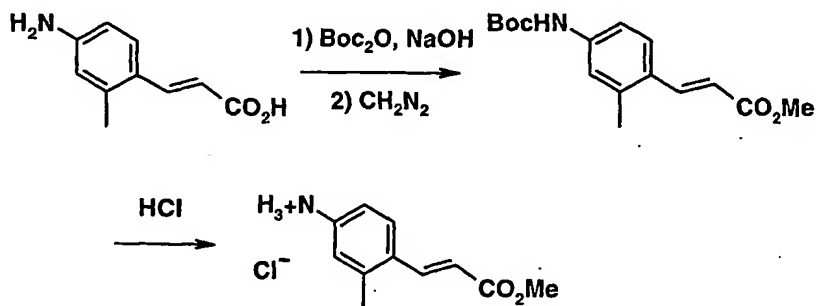


- To a solution of 2-amino-4-methylthiazole (7.90 g, 69 mmol) in Et₂O (70 mL) at 15 °C, Br₂ was added slowly over a period of 30 min while stirring vigorously. The solid material formed was filtered and recrystallized from EtOH. The crystalline product
- 5 was filtered and dried under vacuum to give the 5-bromo derivative as the HBr salt (10.3 g). This product was then dissolved in a solution of CuSO₄ (11.4 g) and NaBr (9.9 g) in H₂O (115 mL) and H₂SO₄ (5M, 360 mL) was added at 0 °C. An aqueous solution of NaNO₂ (6.10 g in 20 mL of H₂O) was then added drop wise to the reaction mixture over a period of 25 min, maintaining the temperature below 3 °C. The
- 10 reaction mixture was stirred at 3 °C for 20 min and then at RT for 1 h. The reaction mixture was diluted with brine (280 mL) and extracted with Et₂O (3 x 300 mL). The ether layers were combined, washed with a saturated, aqueous solution of sodium thiosulfate to eliminate any unreacted Br₂, dried over anhydrous MgSO₄ and filtered through a pad of silica gel (~200 mL). The solvent was evaporated and the desired
- 15 product isolated by distillation (bp = 80-81 °C at 15mm Hg). A solution of the dibromo intermediate (500 mg, 1.94 mmol) in hexane (5 mL) was added to a cooled solution (-70 °C) of *n*-BuLi (870 µL of 2.2M in hexane), diluted with 10 mL of hexane. The reaction was stirred at -70 °C for 1 h and then added to CO₂(s). The mixture was partitioned between H₂O and Et₂O. The aqueous layer was
- 20 acidified with 1N HCl (pH ~2) and extracted with EtOAc (2 x), dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was re-dissolved in MeOH / DCM, treated with CH₂N₂ (until the solution remained yellow) and evaporated to dryness to give the desired 5-bromo-4-methylthiazole-2-carboxylate ester as a yellow solid (230 mg). Suzuki cross-coupling of this product with the *N*-Boc protected 4-
- 25 aminophenylboronic acid, as previously described (example 25), gave the building block 5-(4-amino-phenyl)-4-methyl-thiazole-2-carboxylate methyl ester. This product was treated with 4N HCl in dioxane for 30 min to remove the Boc protecting group and obtain the desired compound.

EXAMPLE 27:**(E)-3-(4-Amino-phenyl)-2-methyl-acrylic acid methyl ester:**

5

α -Methyl-4-nitrocinnamic acid (53 mg, 0.25 mmol) was dissolved in EtOAc and MeOH and a solution of CH_2N_2 in Et_2O was added until a persistent yellow color was observed. A couple of drops of AcOH were added to destroy the excess CH_2N_2 . The mixture was diluted with EtOAc and the organic layer was washed with H_2O , aqueous NaOH (1N) and brine, dried over anhydrous MgSO_4 and concentrated to dryness. The residue was re-dissolved in EtOH (2 mL), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (289 mg, 1.28 mmol) was added and the reaction mixture was heated to reflux for 1h. The mixture was cooled to RT, diluted with EtOAc and quenched by the addition of aqueous, saturated NaHCO_3 . The organic layer was separated, washed with brine, dried over anhydrous MgSO_4 and concentrated to dryness to give the title compound (40 mg) as a yellow solid.

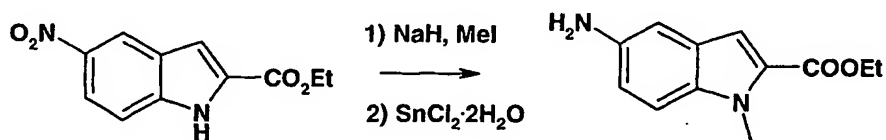
10
15**EXAMPLE 28:****4-((E)-2-Methoxycarbonyl-vinyl)-3-methyl-phenyl-ammonium chloride:**

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4-Amino-2-methyl cinnamic acid (0.090 g, 0.51 mmol) and NaOH (1M, 1.1 mL, 1.1 mmol) were dissolved in dioxane (4 mL), Boc_2O (117 mg, 0.53 mmol) was added and the mixture was stirred at RT for 15 h. The reaction mixture was partitioned between EtOAc and H_2O , the pH of the aqueous layer was adjusted to be basic using 1N NaOH, and extracted with EtOAc (3 x). The aqueous layer was then

25

acidified to pH ~2 and extracted with EtOAc (3 x). The new organic layers were combined, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated to give an orange gum (118 mg). The crude Boc-protected 4-amino-2-methyl cinnamic acid was re-dissolved in EtOAc and a solution of CH_2N_2 in Et_2O was added until a persistent yellow color was observed. A few drops of AcOH were added to destroy the excess CH_2N_2 and the reaction mixture was washed with 10% aqueous HCl, saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated to dryness. Purification by flash column chromatography, using 10% EtOAc in hexane as the eluent, led to the isolation of the Boc-protected methyl ester as a yellow solid (36 mg). Finally, the Boc protecting group was removed after acid treatment with HCl in dioxane (as described previously) to give the title compound.

EXAMPLE 29:***5-Amino-1-methyl-1H-indole-2-carboxylic acid ethyl ester***

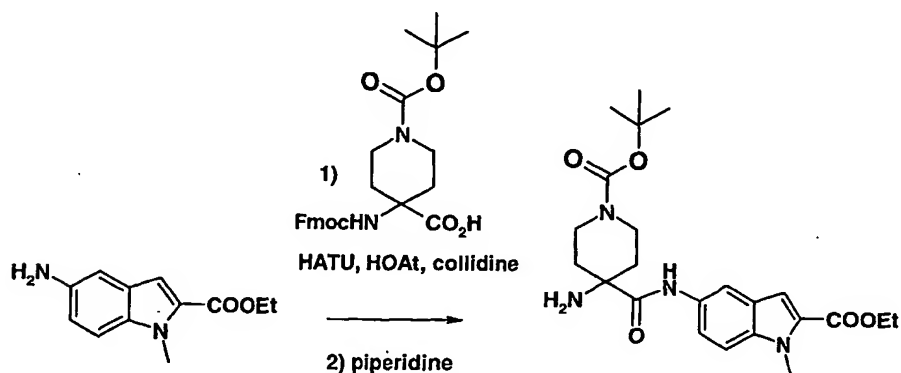
The ethyl ester of 5-nitroindole-2-carboxylic acid (0.300 g, 1.28 mmol) was dissolved in anhydrous DMF (6 mL) and NaH (0.078 g, 60%, 1.92 mmol) was added. The reaction was stirred at RT for 20 min, then MeI (160 μL , 2.56 mmol) was added and stirring was continued for 3 h. The reaction was quenched with the addition of aqueous NaHCO_3 (~1%) while stirring vigorously. The brown solid formed (0.096 g) was filtered and dried in air overnight.

The *N*-methyl nitro derivative (196 mg, 0.79 mmol) was then dissolved in DMF (4 mL), H_2O (400 μL) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (888 mg, 3.95 mmol) were added, and the mixture was stirred at 60 $^\circ\text{C}$ for 3 h. The mixture was then partitioned between 10% aqueous NaHCO_3 and EtOAc and stirred vigorously. The aqueous layer was re-extracted with EtOAc and the combined EtOAc layers were washed with brine, dried over anhydrous MgSO_4 and concentrated to dryness. The residue was purified by flash column chromatography, using 1:1 ratio EtOAc/hexane as the eluent, to obtain the pure 5-aminoindole derivative (118 mg).

N-Alkylation of 5-nitroindole-2-carboxylate with other alkylating agents (such as EtI, propargyl bromide, benzyl bromide) under the conditions described above gave the corresponding 5-amino-1-alkyl-1*H*-indole-2-carboxylates.

5 **EXAMPLE 30:**

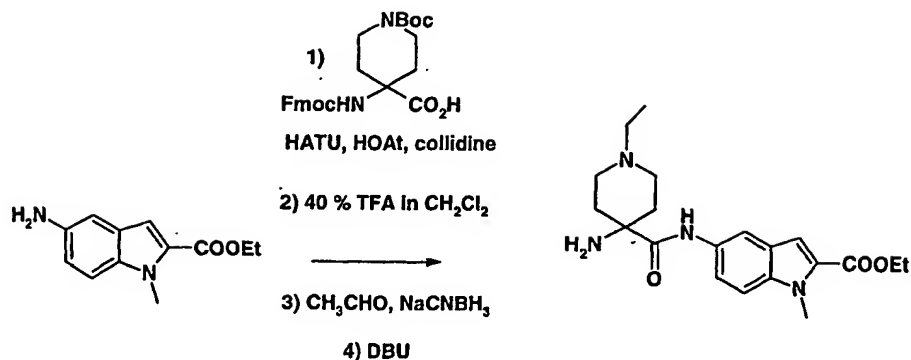
5-[[1-(4-Amino-1-*t*-butoxycarbonyl-piperidin-4-yl)-methanoyl]-amino]-1-methyl-1*H*-indole-2-carboxylic acid ethyl ester:



A solution of amine from example 29 (70 mg, 0.32 mmol), *N*-Fmoc-amino-(4-*N*-Boc-piperidinyl)carboxylic acid (150 mg, 0.32 mmol), HATU (139 mg, 0.35 mmol), HOAt (48 mg, 0.35 mmol) and collidine (155 mg, 1.28 mmol) in DMF (2 mL) was stirred at RT for 15 h. The reaction mixture was diluted with EtOAc, washed with 1% aqueous citric acid (2 x), saturated NaHCO₃ (2 x) and brine, dried over anhydrous MgSO₄ and concentrated to dryness to give an orange solid (210 mg) which was used in the next reaction without purification. A solution of the crude solid (210 mg) in DMF (3 mL) and piperidine (95 mL, 0.95 mmol) was stirred at RT for 3 h. The reaction mixture was concentrated to dryness and purified by flash column chromatography, using a solvent gradient from 50% EtOAc in hexane to 100% EtOAc as the eluent, to give the compound as a brown solid (110 mg).

20 **EXAMPLE 31:**

5-[[1-(4-Amino-1-ethyl-piperidin-4-yl)-methanoyl]-amino]-1-methyl-1*H*-indole-2-carboxylic acid ethyl ester:



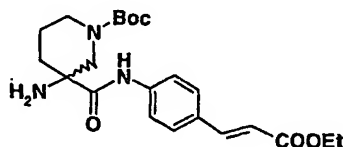
The 5-aminoindole derivative of example 29 was coupled to N-Fmoc-amino-(4-N-Boc-piperidinyl)carboxylic acid as described in example 30.

The Boc protecting group was removed with 25% TFA in CH2Cl2 in the usual way, and the product was then dissolved in EtOH (6 mL). AcOH (133 mg), acetaldehyde (33 mg, 0.74 mmol) and NaCNBH3 (23mg, 0.37 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to remove most of the solvent, the residue was re-dissolved in EtOAc and washed with saturated NaHCO3 and brine. The organic layer was dried over anhydrous MgSO4 and concentrated to give the N-ethyl derivative as an orange solid.

This solid was dissolved in THF (2.5 mL), DBU (113 mg, 0.74 mmol) was added and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, the remaining residue was dissolved in EtOAc and the organic layer was washed with saturated NaHCO3 and brine. The organic layer was further extracted with 1N HCl and H2O (2 x), and the pH of the combined aqueous layers was adjusted to pH ~10 with 1N NaOH. The aqueous layer was then extracted with EtOAc (3 x), the combined organic layers were washed with brine, dried over anhydrous MgSO4 and concentrated to dryness to give the title amine derivative (44 mg).

EXAMPLE 32:

(E)-3-(4-([1-(3-Amino-piperidin-3-yl)-methanoyl]-amino)-phenyl)-acrylic acid ethyl ester:



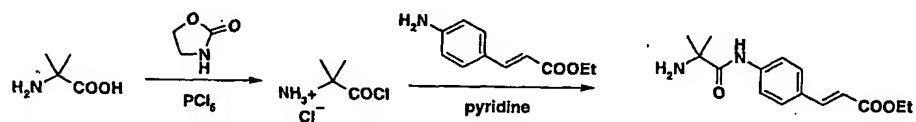
Following a similar procedure to that described in example 31, commercially available N-Fmoc-amino-(3-N-Boc-piperidinyl)carboxylic acid was coupled to the ethyl ester of 4-aminocinnamic acid and the Fmoc protecting group was removed to give the title compound of example 32 in racemic form.

The racemic starting material, N-Fmoc-amino-(3-N-Boc-piperidinyl)carboxylic acid, could also be resolved into its two enantiomers by preparative HPLC on a chiral support (Chiralcel OD, 10 micron, 2.00 cm I.D. x 25 cm), using 35% H₂O in MeCN as the eluent.

EXAMPLE 33:

General procedure for coupling α,α -disubstituted amino acids to aromatic amines:

(E)-3-[4-(2-Amino-2-methyl-propanoylamino)-phenyl]-acrylic acid ethyl ester:

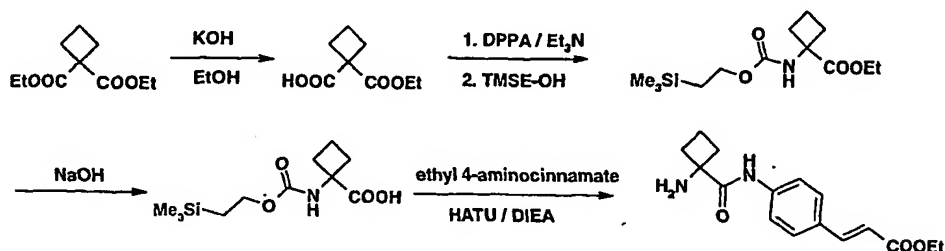


Adapting the procedure described by E. S. Uffelman et al. (*Org. Lett.* **1999**, *1*, 1157), 2-aminoisobutyric acid was converted to the corresponding amino acid chloride hydrochloride: 2-oxazolidinone (12.30 g, 0.141 mole) was dissolved in MeCN (150 mL) and phosphorous pentachloride (49.02 g, 0.235 mole, 1.7 equivalent) was added in one portion. The homogeneous mixture was stirred for 24 h at room temperature. 2-Aminoisobutyric acid (14.55 g, 0.141 mole) was added and the suspension was stirred for 48 h at room temperature. The desired acid chloride hydrochloride was collected by filtration, washed with MeCN and dried under vacuum.

The acid chloride (12.778 g, 80 mmol, 1.4 equivalent) was suspended in DCM (200 mL) and ethyl 4-aminocinnamate (11.045 g, 57.7 mmol, 1 equivalent) was added. Pyridine (7.01 mL, 86.6 mmol, 1.5 equivalent) was added drop wise and the mixture was stirred for 3.5 h at room temperature. The reaction was then poured into a mixture of 1N NaOH (25 mL) and saturated aqueous NaHCO₃ (100 mL) and extracted with EtOAc. The organic phase was washed with aqueous NaHCO₃, water and brine, and dried over MgSO₄. Removal of solvent under reduced pressure gave the title compound as a white solid (15.96 g, 101% yield).

EXAMPLE 34:

(E)-3-(4-[[1-(1-Amino-cyclobutyl)-methanoyl]-amino]-phenyl)-acrylic acid ethyl ester:

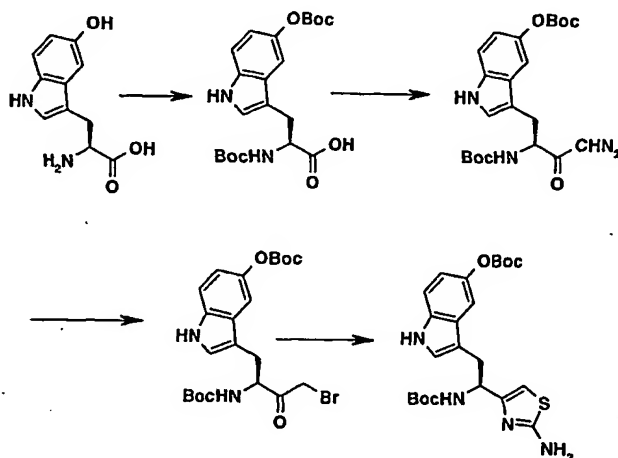


- 5 Diethyl 1,1-cyclobutanedicarboxylate (20.00 g, 100 mmol) and KOH (6.60 g, 100 mmol) were refluxed in EtOH (100 mL) for 2 h. After cooling to room temperature, volatiles were removed under reduced pressure and the residue partitioned between Et₂O and 4N HCl. The organic extract was washed with water and brine, and dried over MgSO₄. Removal of the solvent under reduced pressure gave the monoester as a clear oil (14.45 g, 84% yield).
- 10 The monoester from above (14.45 g, 84 mmol), Et₃N (14.1 mL, 100 mmol) and diphenylphosphoryl azide (24.05 g, 87.4 mmol) were dissolved in dry toluene (114 mL) and the mixture heated at 80 °C for 1 h and 110 °C for an additional hour.
- 15 Trimethylsilylethanol (9.94 g, 100 mmol) was added in one portion and the mixture refluxed for 48 h. Toluene was then removed under reduced pressure and the residue dissolved in DCM. The solution was washed with water and brine and dried over MgSO₄. Concentration under reduced pressure gave a dark oil which was purified by passage through a pad of silica gel using 30% EtOAc in hexane as eluent. The desired carbamate was obtained as a clear yellow liquid (21.0 g).
- 20 The carbamate from above (1.50 g, 5.22 mmol) was dissolved in THF (5 mL) and 2N NaOH (5 mL) was added. The mixture was stirred at 70 °C for 1 h. Following dilution with water, the aqueous phase was washed with Et₂O to remove unreacted starting material. The aqueous phase was then acidified with KHSO₄ and the
- 25 product extracted with EtOAc. The desired free carboxylic acid was obtained as an oil (1.25 g).
- The acid from above (0.519 g, 2.0 mmol) was dissolved in DCM (10 mL). DIEA (1.39 mL, 8.0 mmol, 4 equivalents) was added, followed by ethyl 4-aminocinnamate
- 30 (0.573 g, 3.0 mmol, 1.5 equivalent) and HATU (1.143 g, 3.0 mmol, 1.5 equivalents).

The mixture was stirred at room temperature for 3 days. The reaction was poured into TBME (100 mL) and the solution washed successively with 10% aqueous citric acid (2 x 25 mL) and saturated aqueous NaHCO₃ (25 mL), and dried over MgSO₄. The solvent was removed under reduced pressure and the residue stirred with TFA (10 mL) for 30 min. Volatiles were then removed under reduced pressure and the residue was co-evaporated twice with hexane. The crude product was dissolved in TBME (60 mL) and the solution washed with 1N NaOH (2 x 25 mL). After drying (Na₂SO₄), volatiles were removed in vacuum to give the title compound as a light brown solid (0.500 g).

10 **EXAMPLE 35:**

Carbonic acid 3-[(S)-2-tert-butoxycarbonylamino-2-(2-amino-thiazol-4-yl)-ethyl]-1H-indol-5-yl ester tert-butyl ester:



(S)-5-Hydroxytryptophan was converted to the bis-Boc derivative by the method of V. F. Pozdnev, *Chem. Nat. Compd. (Engl. Transl.)* **1982**, *18* (1), 125) which was isolated as the free carboxylic acid. This material (1.0377 g, 2.47 mmol) was dissolved in THF (5 mL), DIEA (0.645 mL, 3.7 mmol) was added and the mixture cooled in ice. Isobutyl chloroformate (0.384 mL, 2.96 mmol) was added and the mixture stirred at 0-5 °C for 18 h. Excess diazomethane in Et₂O (0.6 M, 15 mL) was then added and the mixture stirred for 1 h. Another portion of diazomethane (10 mL) was added and after 40 min, the reaction was diluted with Et₂O (75 mL). The solution was washed successively with 10% aqueous citric acid (25 mL) and saturated aqueous NaHCO₃ (25 mL), and dried (MgSO₄). Volatiles were removed under reduced pressure and the residue purified by flash chromatography with 40% EtOAc / hexane. The diazomethylketone was obtained as a yellow foam (0.783 g).

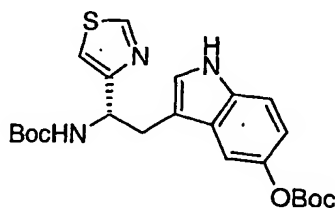
The diazomethylketone from above was dissolved in EtOAc (10 mL) and the solution cooled to -30°C . A solution of HBr in AcOH (48% w/w, 0.384 mL) was added dropwise over 60 min. The cold reaction mixture was then diluted with Et₂O (100 mL) and washed successively with 10% aqueous citric acid (2 X 25 mL) and saturated aqueous NaHCO₃ (25 mL), and dried (MgSO₄). Volatiles were removed under reduced pressure and the residue coevaporated with hexane to give the bromomethylketone as a white foam (0.870 g).

The bromomethylketone from above was reacted with thiourea (2 equivalents) in MeCN at room temperature for 18 h. The solvent was then removed under reduced pressure and the residue dissolved in minimal DMSO. This solution was added dropwise with stirring to a mixture of water (15 mL) and DIEA (0.2 mL). The precipitate that formed was collected by filtration, washed with water and dried to give the title compound.

This method is general and can be applied to the preparation of other 2-alkyl and 2-alkylaminothiazole derivatives by reacting the appropriate thioamide or thiourea derivative with the bromomethylketone compound described above.

EXAMPLE 36:

Carbonic acid 3-((S)-2-tert-butoxycarbonylamino-2-thiazol-4-yl-ethyl)-1H-indol-5-yl ester tert-butyl ester:



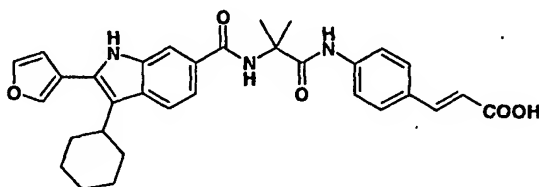
To a stirred suspension of P₂S₅ (0.89 g, 2.0 mmol) in dry dioxane (5 mL) was added dry formamide (433 μL , 10.9 mmol). The mixture was heated at 90°C for 2.5 h (to maintain a free suspension occasional trituration was needed). The suspension was allowed to cool to room temperature, the solid filtered off and the bromoketone from example 29 (0.5 mmol) was added to the filtrate. The solution was heated to 80°C for 2 h then diluted with EtOAc (25 mL), washed with 5% aqueous citric acid (2 X 20 mL), 5% aqueous sodium bicarbonate (2 X 20 mL) and brine. After drying (MgSO₄) and removal of the solvent under reduced pressure, the title compound was obtained.

EXAMPLE 37 (ENTRY 2050):

General procedure for coupling 5- or 6-indolecarboxylic acids to α,α -disubstituted amino amides:

5

(E)-3-[4-(2-([1-(3-Cyclohexyl-2-furan-3-yl)-1H-indol-6-yl)-methanoyl]-amino)-2-methyl-propanoylamino]-phenyl]-acrylic acid:

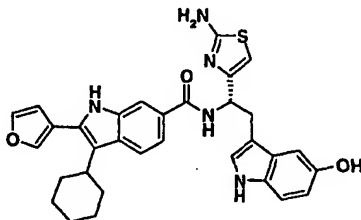


10

The indole carboxylic acid derived from the methyl ester of example 3 (0.050 g, 0.16 mmol), the amino amide derivative of example 33 (0.053 g, 0.019 mmol, 1.2 equivalent) and HATU (0.122 g, 0.32 mmol, 2 equivalents) were dissolved in DMSO (1 mL). DIEA (0.14 mL, 0.8 mmol, 5 equivalents) was added. The mixture was stirred for 1 h at room temperature then treated with 2.5N NaOH (0.3 mL) for 1 h at 50 °C to affect hydrolysis of the cinnamate ester function. The mixture was then acidified to pH 1 with TFA and the title compound was isolated by preparative reversed-phase HPLC (0.033 g).

EXAMPLE 38 (ENTRY 1010):

General procedure for coupling thiazole derivatives (Examples 35, 36) to 6-indolecarboxylic acids:



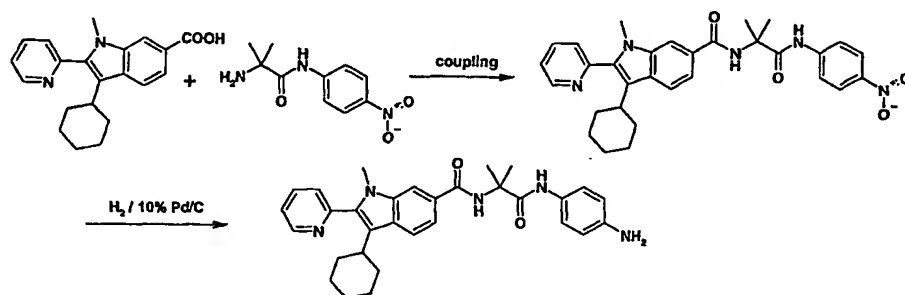
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The thiazole derivative of example 35 was deprotected by stirring with 4 N HCl in dioxane and coupled to the 6-indole carboxylic acid derived from the methyl ester of

example 3 using TBTU/DIEA in DMSO as described in example 37. Following coupling, the title compound was isolated directly by preparative reversed-phase HPLC.

5 EXAMPLE 39

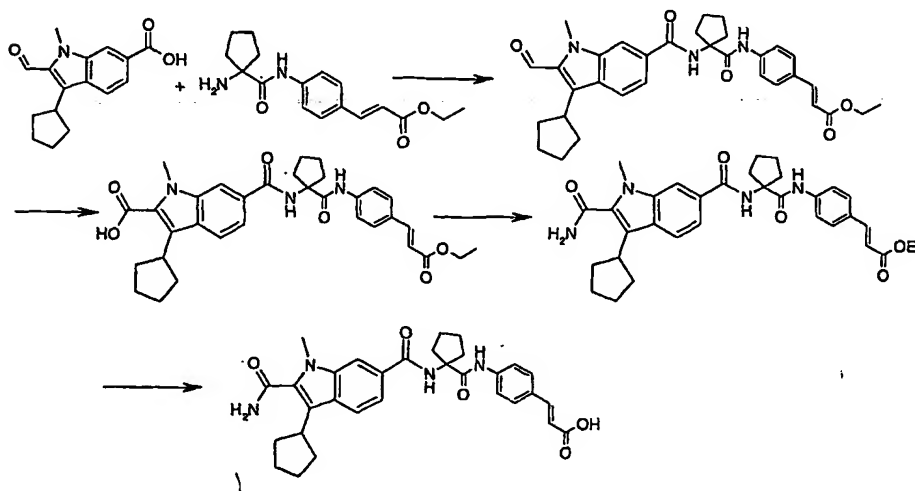
3-Cyclohexyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid [1-(4-amino-phenylcarbonyl)-1-methyl-ethyl]-amide (Entry 2072):



- The amino amide derivative prepared from α -aminoisobutyryl chloride and 4-nitroaniline following the procedure of example 33 was coupled in the usual way (example 37) to the indole derivative of example 9.
- The nitro derivative was hydrogenolyzed (1 atm H_2 gas, 10% Pd/C) in MeOH for 5 h to give the title compound after purification by preparative reversed-phase HPLC.

15 EXAMPLE 40

(E)-3-(4-[[1-(1-[[1-(2-Carbamoyl-3-cyclopentyl-1-methyl-1H-indol-6-yl)-methanoyl]-amino)-cyclopentyl]-methanoyl]-amino)-phenyl)-acrylic acid:



To a mixture of the acid aldehyde, derived by saponification of the ester aldehyde of example 16, (50 mg, 0.184 mmol) and an amine, prepared adapting the procedure described in example 33, (55.7 mg, 0.184 mmol) in CH₂Cl₂ were successively added
5 HATU (84 mg, 0.221 mmol) and DIEA (128 µL, 0.736 mmol). The reaction mixture was stirred overnight at room temperature and then concentrated. The residue was dissolved in EtOAc and successively washed with a 10 % aq. citric acid solution (2X), a satd aq. NaHCO₃ solution, water and then with brine. After the usual treatment (MgSO₄, filtration and concentration) the residue was flash
10 chromatographed (2 cm, 35 % AcOEt-hexane) to afford the desired amide-aldehyde derivative (83.5 mg, 0.150 mmol, 81.5 % yield).

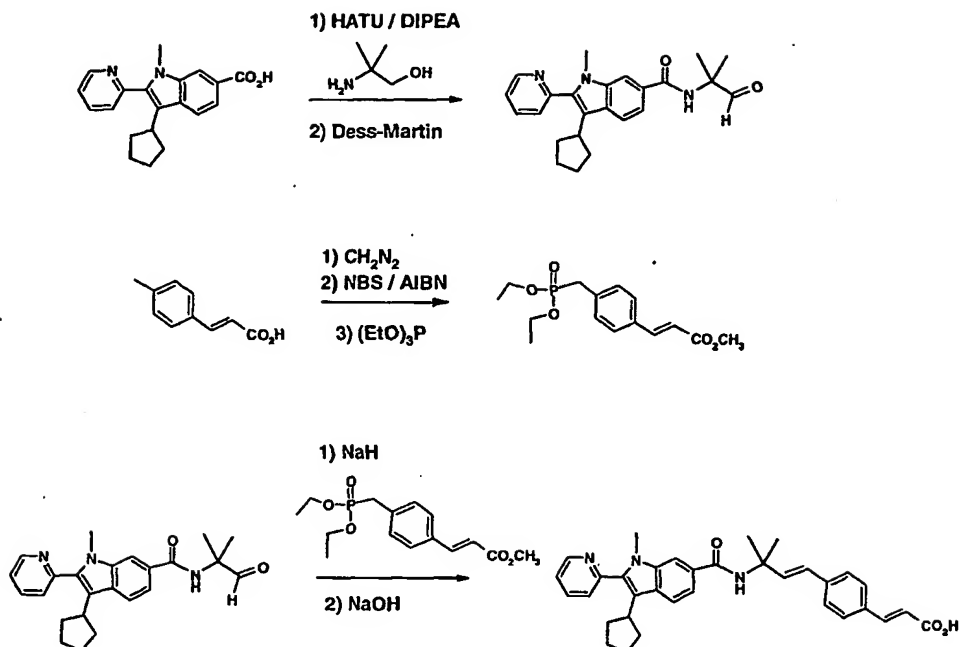
To the aldehyde from above (87 mg, 0.157 mmol) in a mixture of *tert*-butanol (2 mL) and 2-methyl-2-butene (1.2 mL) at 0 °C was added a freshly prepared solution of sodium chlorite (141.6 mg, 1.57 mmol) in phosphate buffer (216 mg of NaH₂PO₄,
15 1.57 mmol, in 600 µL of water). The reaction mixture was stirred for 10 min. at room temperature then brine was added. The mixture was extracted with EtOAc (2X) and the combined organic layers were successively washed with a 0.5 N aq. solution and brine. After the usual treatment (MgSO₄, filtration and concentration) the crude desired acid was isolated as a white solid (82.6 mg, 92.3 % yield).

To the acid (15 mg, 0.0275 mmol) in DMF at 0 °C were successively added DIEA (7.2 µL, 0.0413 mmol) and isobutyl chloroformate (10.7 µL, 0.0413 mmol). The reaction mixture was stirred for 30 min at this temperature then ammonium hydroxide (7.5 µL, 0.056 mmol) was added. After the addition the mixture was slowly allowed to warm to room temperature and stirred overnight. 1N aq. NaOH was
25 added (275 µL, 0.275 mmol) and the reaction mixture was heated at 60 °C for 1.5 h. Glacial acetic acid was finally added to destroy the excess hydroxide and the mixture was HPLC purified. After lyophilization the desired amide was isolated (2.6 mg, 0.005 mmol, 18 % yield) as a white solid.

Other 2-carboxamide derivatives were prepared in a similar fashion by replacing ammonia with the desired amine.
30

EXAMPLE 41

(E)-3-[4-((E)-3-[[1-(3-Cyclopentyl-1-methyl-2-pyridin-2-yl)-1H-indol-6-yl]-methanoyl]-amino)-3-methyl-but-1-enyl]-phenyl]-acrylic acid:



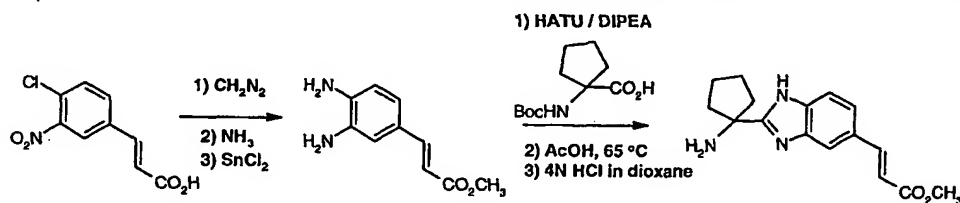
- 3-Cyclopentyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid (0.100 g, 0.31 mmol), 2-amino-2-methyl-1-propanol (0.028 g, 0.31 mmol) and HATU (0.154 g, 0.41 mmol) were dissolved in DMSO (5 mL). To this mixture, DIEA (0.22 mL, 1.2 mmol) was added and the solution was stirred at room temperature for 3 h. The reaction mixture was poured into EtOAc (100 mL) and the solution washed successively with saturated aqueous NaHCO_3 (2 x 25 mL) and brine (25 mL), and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (using 60-70% EtOAc in hexane) to give the primary alcohol intermediate as a yellow oil (0.048 g). This product was dissolved in CH_2Cl_2 (2 mL), Dess-Martin periodinane (0.063 g, 0.15 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with CH_2Cl_2 (100 mL), the organic layer was dried over anhydrous MgSO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (using 60% EtOAc in hexane) to give the aldehyde intermediate (0.011 g).
- Diazomethane was slowly added to a solution of 4-methylcinnamic acid (3.0 g, 18.5 mmol) in $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ (5 mL/15 mL) until the yellow color persisted, indicating the presence of excess diazomethane. The solution was evaporated to dryness under reduced pressure and the residue was re-dissolved in CCl_4 (15 mL). *N*-Bromosuccinimide (3.62 g, 20.4 mmol) and AIBN (0.304 g, 1.85 mmol) were added

and the mixture was stirred at reflux for 3 hours. The solution was then cooled to room temperature and filtered. The organic layer was washed with aqueous NaOH (0.5 N, 2 x 50 mL) and water (50 mL), dried over anhydrous MgSO_4 and filtered. The solvent was removed under vacuum and the residue was purified by flash column chromatography (0-40% EtOAc in hexane) to obtain the bromide intermediate as a white solid (2.4 g). This product was dissolved in $(\text{EtO})_3\text{P}$ (37.7 mL, 220 mmol) and heated to reflux at 160 °C. The ethyl bromide formed was collected in a Dean-Stark distillation apparatus over a period of 2.5 hours. The reaction mixture was condensed under vacuum to a yellow solid, which was then purified by flash column chromatography (70-100% EtOAc in hexane) to give the phosphonate as a white solid (1.9 g).

A solution of phosphonate (20 mg, 0.06 mmol) and NaH (60%, 3.5 mg, 0.087 mmol) in anhydrous THF (300 μL) was stirred at RT for 30 min. A solution of the aldehyde intermediate (11 mg, 0.029 mmol) in THF was added and stirring was continued for 4 hours. After that period, aqueous NaOH (2.5 N, 50 μL) was added and the mixture was stirred at 40 °C for 15 hours. The mixture was acidified with glacial acetic acid (~1 mL), concentrated and purified by reversed HPLC to obtain the title compound (3.7 mg) as a yellow solid.

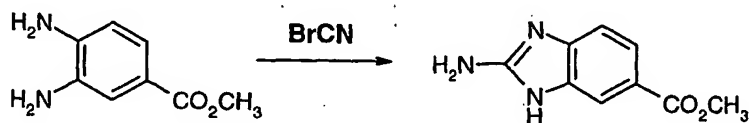
20 EXAMPLE 42:

(Z)-3-[2-(1-Amino-cyclopentyl)-1H-benzimidazol-5-yl]-acrylic acid methyl ester:



Diazomethane was slowly added to a solution of 4-chloro-3-nitrocinnamic acid in $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ until the yellow color persisted, indicating the presence of excess diazomethane. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in DMSO. The solution was heated to 140 °C and ammonia gas was bubbled through for a period of 4 hours. The mixture was cooled to room temperature and degassed with N_2 , and poured onto ice. The precipitate formed was filtered, washed with cold water and dried under vacuum for 16 hours to give the crude 4-amino-3-nitrocinnamic ester as a yellow solid (2.05 g). The solid

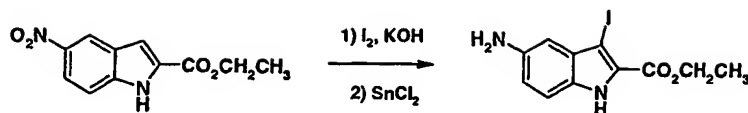
- was dissolved in ethanol (40 mL), $\text{SnCl}_2 \cdot \text{dihydrate}$ (9.91 g, 43.9 mmol) was added and the reaction mixture was heated to reflux for 4 hours. The solution was concentrated to remove most of the ethanol, diluted with EtOAc and saturated aqueous NaHCO_3 was added slowly. The mixture was stirred for 20 min, the organic layer was extracted with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (using 50% to 70% EtOAc in hexane) to give the diamino intermediate as a yellow solid (1.03 g).
- A portion of the 3,4-diaminocinnamate ester (186 mg, 0.970 mmol) and N-Boc-1-aminocyclopentane-1-carboxylic acid (222 mg, 0.970 mmol) were coupled in the presence of HATU / DIEA (in the usual way) and the amide product formed was dehydrated by heating at 65 °C in a solution of acetic acid (4 mL). The reaction residue was purified by reversed HPLC to give the N-Boc protected (Z)-3-[2-(1-amino-cyclopentyl)-1H-benzoimidazol-5-yl]-acrylic acid ethyl ester.
- The Boc protecting group was removed with 4N HCl in dioxane in the usual way to give (Z)-3-[2-(1-amino-cyclopentyl)-1H-benzoimidazol-5-yl]-acrylic acid ethyl ester as yellow foam (200 mg).

EXAMPLE 43:**20 2-Amino-3H-benzoimidazole-5-carboxylic acid:**

- A solution of cyanogen bromide (5M, 1.44 mL, 7.22 mmol) was slowly added to a suspension of 3,4-diaminobenzoate (1.0 g, 6.02 mmol) in water (10 mL). The mixture was stirred at room temperature for 24 hours. An aqueous solution of Na_2CO_3 (10%) was added slowly until the product had precipitated as a brown solid (890 mg).

30 EXAMPLE 44:**5-Amino-3-iodo-1H-indole-2-carboxylic acid ethyl ester:**

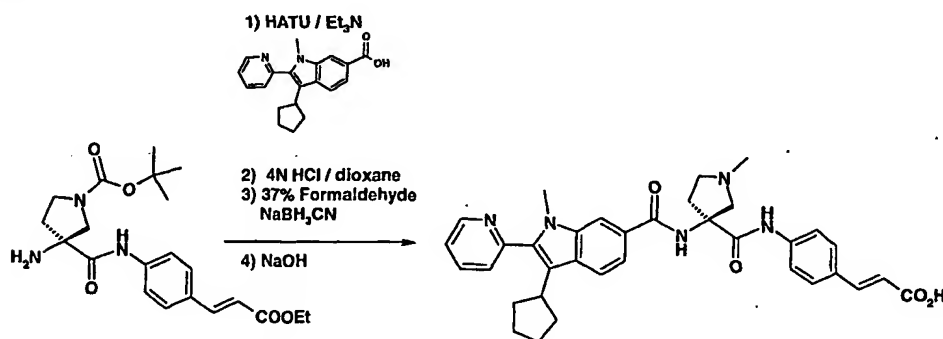
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Ethyl 5-nitroindole-2-carboxylate (1.00 g, 4.27 mmol) was dissolved in DMF (15 mL), KOH (0.84 g, 14.9 mmol) was added and the mixture was stirred at room temperature for 10 min. Iodine (1.084 g, 4.27 mmol) was added and stirring was continued for 3 hours. The reaction mixture was poured into a solution of water (150 mL) containing $NaHSO_3$ (1 g) and concentrated NH_4OH (2.5 mL). The precipitate formed was filtered, washed with water and dried to give the 3-iodo intermediate as a beige solid (1.49 g). A portion of this solid (503 mg, ~1.4 mmol) was dissolved in ethanol (15 mL), $SnCl_2 \cdot dihydrate$ (1.58 g, 6.99 mmol) was added and the reaction mixture was heated to reflux for 4 hours. The solution was concentrated to remove most of the ethanol, diluted with EtOAc and saturated aqueous $NaHCO_3$ was added slowly to pH=8-9. The mixture was stirred for 20 min, the organic layer was extracted with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue (431 mg of brown solid) contained the desired product 5-amino-3-iodo-1H-indole-2-carboxylic acid ethyl ester in reasonable purity to be used in the synthesis of inhibitors without further purification.

EXAMPLE 45:

(E)-3-(4-([1-((S)-3-([1-(3-Cyclopentyl-1-methyl-2-pyridin-2-yl)-1H-indol-6-yl)-methanoyl]-amino)-1-methyl-pyrrolidin-3-yl)-methanoyl]-amino)-phenyl)-acrylic acid:



3-Cyclopentyl-1-methyl-2-pyridin-2-yl-1H-indole-6-carboxylic acid (0.197 mg, 0.589 mmol), the appropriate amine (0.170 g, 0.420 mmol) and HATU (0.320 g, 0.840 mmol) were dissolved in DMSO (4 mL). To this mixture, Et_3N (0.300 mL, 2.15 mmol) was added and the solution was stirred at room temperature for 5 hours. The

reaction mixture was poured into EtOAc (100 mL) and the solution washed successively with 1% aqueous citric acid (2 x 25 mL), saturated aqueous NaHCO₃ (2 x 25 mL) and brine (25 mL), and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (using hexane/EtOAc in 1:1 ratio) to give the intermediate product as a slightly colored foam (280 mg). This product was stirred in 4N HCl in dioxane (3.0 mL) for 1 hour (to remove the Boc protecting group) and then all volatile components were removed under reduced pressure.

A portion of the residue (41 mg, 0.060 mmol) was dissolved in ethanol (2 mL), acetic acid (31 mg, 0.530 mmol) was added, 37% aqueous formaldehyde (15 µL, ~0.2 mmol) and NaBH₃CN (5.6 mg, 0.090 mmol) and the mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the residue was re-dissolved in DMSO (1 mL), aqueous NaOH (2.5 N, 230 µL, 0.58 mmol) was added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified by the addition of acetic acid (~1 mL) and purified by C18 reversed phase preparative HPLC to give the final product as a light yellow solid (11 mg).

EXAMPLE 46: INHIBITION OF NS5B RNA DEPENDENT RNA POLYMERASE ACTIVITY

- The compounds of the invention were tested for inhibitory activity against the hepatitis C virus RNA dependant polymerase (NS5B), according to the following assay:
- The substrates are:
- a 12 nucleotide RNA oligo-uridylate (or oligo-uridine-monophosphate) (oligo-U)
 - primer modified with biotin at the free 5'C position;
 - a complementary poly-adenylate (or adenosine monophosphate) (polyA) template of heterogeneous length (1000-10000 nucleotides); and
 - UTP-[5,6 ³H].
- Polymerase activity is measured as the incorporation of UMP-[5,6 ³H] into the chain elongated from the oligo-U primer. The ³H-labelled reaction product is captured by SPA-beads coated with streptavidin and quantified on the TopCount.

All solutions were made from DEPC treated MilliQ water [2 ml of DEPC is added to 1 L of MilliQ water; the mixture is shaken vigorously to dissolve the DEPC, then autoclaved at 121°C for 30 minutes].

Enzyme: The full length HCV NS5B (SEQ ID NO.1) was purified as an N-terminal hexa-histidine fusion protein from baculovirus infected insect cells. The enzyme can be stored at -20°C in storage buffer (see below). Under these conditions, it was
5 found to maintain activity for at least 6 months.

Substrates: The biotinylated oligo- U_{12} primer, the Poly(A) template, and the UTP- $[5,6\text{ }^3\text{H}]$ were dissolved in water. The solutions can be stored at -80°C .

10	Assay buffer: 20 mM Tris-HCl pH 7.5 5 mM MgCl_2 25 mM KCl 1 mM EDTA 1 mM DTT
15	NS5B storage buffer: 0.1 μM NS5B 25 mM Tris-HCl pH 7.5 300 mM NaCl 5 mM DTT 1 mM EDTA 0.1 % n-Dodecyl maltoside 30 % glycerol
20	

Test compound cocktail: Just prior to assay, test compounds of the invention were dissolved in assay buffer containing 15% DMSO.
25

Substrate cocktail: Just prior to assay, the substrates were mixed in assay buffer to the following concentrations:

Component	Concentration in substrate cocktail	Final Concentration in assay
RNAasin TM	0.5 U/ μL	1.67 U/ μL
Biotin-oligo- U_{12}	3 ng/ μL	1 ng/ μL

140

primer		
PolyA template	30 ng/ μ L	10 ng/ μ L
UTP-[5,6- ³ H] 35 Ci/mmol	0.025 μ Ci/ μ L	0.0083 μ Ci/ μ L 0.25 μ M
UTP	2.25 μ M	0.75 μ M

Enzyme cocktail: Just prior to assay, the RNA polymerase (NS5B) cocktail was prepared in assay buffer to the following specifications:

Component	Concentration in cocktail
Tris-HCl at pH 7.5	20 mM
MgCl ₂	5 mM
KCl	25 mM
EDTA	1 mM
DTT	1 mM
n- Dodecyl maltoside	1%
NS5B	30 nM

5

Protocol:

The assay reaction was performed in a Microfluor™ white "U" bottom plate (Dynatech™ #7105), by successively adding:

20 μ L of test compound cocktail;

10 20 μ L of substrate cocktail; and

20 μ L of enzyme cocktail

(final [NS5B] in assay = 10 nM; final [n-dodecyl maltoside] in assay = 0.33%; final DMSO in assay = 5%).

The reaction was incubated at room temperature for 1.5 hours. STOP solution (20
15 μ L; 0.5 M EDTA, 150 ng/ μ l tRNA) was added, followed by 30 μ l streptavidin coated
PVT beads (8mg/ml in 20 mM Tris-HCl, pH 7.5, 25 mM KCl, 0.025% NaN₃). The
plate was then shaken for 30 minutes. A solution of CsCl was added (70 μ L, 5 M), to
bring the CsCl concentration to 1.95 M. The mixture was then allowed to stand for 1
hour. The beads were then counted on a Hewlett Packard TopCount™ instrument
20 using the following protocol:

Data mode: counts per minute

Scintillator: liq/plast

Energy range: low

Efficiency mode: normal

Region: 0-50

5 Count delay: 5 minutes

Count time: 1 minute

Expected results: 6000 cpm/well

200 cpm/well no enzyme control.

10 Based on the results at ten different concentrations of test compound, standard concentration-% inhibition curves were plotted and analysed to determine IC_{50} 's for the compounds of the invention. For some compounds the IC_{50} was estimated from two points.

15 **EXAMPLE 47: SPECIFICITY OF NS5B RNA DEPENDENT RNA POLYMERASE INHIBITION**

The compounds of the invention were tested for inhibitory activity against polio virus RNA dependent RNA polymerase and calf thymus DNA dependent RNA polymerase II in the format that is described for the HCV polymerase with the exception that another polymerase was used in place of the HCV NS5B polymerase.

20 **EXAMPLE 48: CELL BASED HCV RNA REPLICATION ASSAY**

Cell Culture

Huh7 cells that stably maintain a subgenomic HCV replicon were established as previously described (Lohman et al., 1999. Science **285**: 110-113) and designated
25 as the S22.3 cell-line. S22.3 cells are maintained in Dulbecco's Modified Earle Medium (DMEM) supplemented with 10% FBS and 1mg/mL neomycin (Standard Medium). During the assay, DMEM medium supplemented with 10% FBS, containing 0.5% DMSO and lacking neomycin was used (Assay Medium). 16 hours
prior to compound addition, S22.3 cells are trypsinized and diluted to 50 000 cells/ml
30 in Standard Medium. 200 μ L (10 000 cells) are distributed into each well of a 96-well plate. The plate was then incubated at 37°C with 5% CO₂ until the next day.

Reagents and Materials:

Product	Company	Catalog #	Storage
DMEM	Wisent Inc.	10013CV	4°C
DMSO	Sigma	D-2650	RT
Dulbecco's PBS	Gibco-BRL	14190-136	RT
Fetal Bovine Serum	Bio-Whittaker	14-901F	-20°C/4°C
Neomycin (G418)	Gibco-BRL	10131-027	-20°C/4°C
Trypsin-EDTA	Gibco-BRL	25300-054	-20°C/4°C
96-well plates	Costar	3997	RT
PVDF 0.22µm Filter Unit	Millipore	SLGV025LS	RT
Deep-Well Titer Plate Polypropylene	Beckman	267007	RT

Preparation of Test Compound

10µL of test compound (in 100% DMSO) was added to 2 ml of Assay Medium for a final DMSO concentration of 0.5% and the solution was sonicated for 15 min and
5 filtered through a 0.22µm Millipore Filter Unit. 900µl was transferred into row A of a Polypropylene Deep-Well Titer Plate. Rows B to H, contain 400µL aliquots of Assay Medium (containing 0.5% DMSO), and are used to prepare serial dilutions (1/2) by transferring 400µl from row to row (no compound was included in row H).

10 Application of test compound to cells

Cell culture medium was aspirated from the 96-well plate containing the S22.3 cells. 175µL of assay medium with the appropriate dilution of test compound was transferred from each well of the compound plate to the corresponding well of the cell culture plate (row H was used as the "No inhibition control"). The cell culture
15 plate was incubated at 37°C with 5% CO₂ for 72 hours.

Extraction of Total Cellular RNA

Following the 72 hour incubation period, the total cellular RNA was extracted from the S22.3 cells of the 96-well plate using the RNeasy 96 kit (Qiagen®, RNeasy
20 Handbook. 1999.). Briefly, assay medium was completely removed from cells and 100 µL of RLT buffer (Qiagen®) containing 143 mM β-mercaptoethanol was added to each well of the 96-well cell-culture plate. The microplate was gently shaken for 20 sec. 100 µL of 70% ethanol was then added to each microplate well, and mixed by

pipetting. The lysate was removed and applied to the wells of a RNeasy 96 (Qiagen®) plate that was placed on top of a Qiagen® Square-Well Block. The RNeasy 96 plate was sealed with tape and the Square-Well Block with the RNeasy 96 plate was loaded into the holder and placed in a rotor bucket of a 4K15C
5 centrifuge. The sample was centrifuged at 6000 rpm (~5600 x g) for 4 min at room temperature. The tape was removed from the plate and 0.8 ml of Buffer RW1 (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The RNeasy 96 plate was placed on top of another
10 clean Square-Well Block, the tape removed and 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The tape was removed and another 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The
15 RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 10 min at room temperature. Tape was removed, the RNeasy 96 plate was placed on top of a rack containing 1.2-mL collection microtubes. The RNA was eluted by adding 50 µL of RNase-free water to each well, sealing plate with a new piece of tape and incubated for 1 min at room temperature. The plate was then
20 centrifuged at 6000 rpm for 4 min at room temperature. The elution step was repeated with a second volume of 50 µl RNase-free water. The microtubes with total cellular RNA are stored at -70°C.

Quantification of Total Cellular RNA

25 RNA was quantified on the STORM® system (Molecular Dynamics®) using the RiboGreen® RNA Quantification Kit (Molecular Probes®). Briefly, the RiboGreen reagent was diluted 200-fold in TE (10mM Tris-HCl pH =7.5, 1mM EDTA). Generally, 50µL of reagent was diluted in 10mL TE. A Standard Curve of ribosomal RNA was diluted in TE to 2µg/mL and pre-determined amounts (100, 50, 40, 20, 10, 5, 2 and
30 0µL) of the ribosomal RNA solution are then transferred in a new 96-well plate (COSTAR # 3997) and the volume was completed to 100µL with TE. Generally, column 1 of the 96-well plate was used for the standard curve and the other wells are used for the RNA samples to be quantified. 10µL of each RNA sample that was to be quantified, was transferred to the corresponding well of the 96-well plate and
35 90µL of TE was added. One volume (100µL) of diluted RiboGreen reagent was

added to each well of the 96-well plate and incubated for 2 to 5 minutes at room temperature, protected from light (a 10 μ L RNA sample in a 200 μ L final volume generates a 20 X dilution). The fluorescence intensity of each well was measured on the STORM® system (Molecular Dynamics®). A standard curve was created on the basis of the known quantities of the ribosomal RNA and the resulting fluorescent intensities. The RNA concentration in the experimental samples was determined from the standard curve and corrected for the 20X dilution.

Reagents and Materials:

Product	Company	Catalog #	Storage
DEPC	Sigma	D5758	4°C
EDTA	Sigma	E5134	RT
Trizma-Base	Sigma	T8524	RT
Trizma-HCl	Sigma	T7149	RT
Collection Tube Strips	Qiagen	19562	RT
Ribogreen RNA Quantitation Kit	Molecular Probe	R11490	-20°C
Rneasy 96 Kit	Qiagen	74183	RT
Square-Well Blocks	Qiagen	19573	RT

Real-Time RT-PCR

The Real-Time RT-PCR was performed on the ABI Prism 7700 Sequence Detection System using the TaqMan EZ RT-PCR Kit from (Perkin-Elmer Applied Biosystems®). RT-PCR was optimized for the quantification of the 5' IRES of HCV RNA by using the Taqman technology (Roche Molecular Diagnostics Systems) similar to the technique previously described (Martell et al., 1999. J. Clin. Microbiol. 37: 327-332). The system exploits the 5'-3' nucleolytic activity of AmpliTaq DNA polymerase. Briefly, the method utilizes a dual-labeled fluorogenic hybridization probe (PUTR Probe) that specifically anneals to the template between the PCR primers (primers 8125 and 7028). The 5' end of the probe contains a fluorescent reporter (6-carboxyfluorescein [FAM]) and the 3' end contains a fluorescent quencher (6-carboxytetramethylrhodamine [TAMRA]). The FAM reporter's emission spectrum was suppressed by the quencher on the intact hybridization probe. Nuclease degradation of the hybridization probe releases the reporter, resulting in an increase

- in fluorescence emission. The ABI Prism 7700 sequence detector measures the increase in fluorescence emission continuously during the PCR amplification such that the amplified product was directly proportion to the signal. The amplification plot was analysed early in the reaction at a point that represents the logarithmic phase of product accumulation. A point representing a defined detection threshold of the increase in the fluorescent signal associated with the exponential growth of the PCR product for the sequence detector was defined as the cycle threshold (C_T). C_T values are inversely proportional to the quantity of input HCV RNA; such that under identical PCR conditions, the larger the starting concentration of HCV RNA, the lower the C_T .
- 5 A standard curve was created automatically by the ABI Prism 7700 detection system by plotting the C_T against each standard dilution of known HCV RNA concentration. Reference samples for the standard curve are included on each RT-PCR plate. HCV Replicon RNA was synthesized (by T7 transcription) *in vitro*, purified and quantified by OD₂₆₀. Considering that 1 µg of this RNA = 2.15×10^{11} RNA copies, dilutions are
- 10 made in order to have 10^8 , 10^7 , 10^6 , 10^5 , 10^4 , 10^3 or 10^2 genomic RNA copies / 5 µL. Total cellular Huh-7 RNA was also incorporated with each dilution (50 ng / 5 µL). 5 µL of each reference standard (HCV Replicon + Huh-7 RNA) was combined with 45 µL of Reagent Mix, and used in the Real-Time RT-PCR reaction.
- 15 The Real-Time RT-PCR reaction was set-up for the experimental samples that were purified on RNeasy 96 –well plates by combining 5 µl of each total cellular RNA sample with 45 µL of Reagent Mix.
- 20

Reagents and Materials:

Product	Company	Catalog #	Storage
TaqMan EZ RT-PCR Kit	PE Applied Biosystems	N808-0236	-20°C
MicroAmp Optical Caps	PE Applied Biosystems	N801-0935	RT
MicroAmp Optical 96-Well Reaction Plate	PE Applied Biosystems	N801-0560	RT

25 Reagent Mix preparation:

Component	Volume for one sample (µL)	Volume for One Plate (µL) (91 samples + Dead Volume)	Final conc.
Rnase-free water	16.5	1617	

5X TaqMan EZ buffer	10	980	1X
Mn(OAc) ₂ (25mM)	6	588	3mM
dATP (10mM)	1.5	147	300μM
dCTP (10mM)	1.5	147	300μM
dGTP (10mM)	1.5	147	300μM
dUTP (20mM)	1.5	147	600μM
Forward Primer (10μM)	1	98	200nM
Reverse Primer (10μM)	1	98	200nM
PUTR probe (5μM)	2	196	200nM
rTth DNA polymerase (2.5 U/μL)	2	196	0.1 U/μL
AmpErase UNG (1U/μL)	0.5	49	0.01 U/μL
Total Volume	45	4410	

Forward Primer Sequence (SEQ ID. 2): 5' - ACG CAG AAA GCG TCT AGC CAT
GGC GTT AGT - 3'

- 5 **Reverse Primer Sequence (SEQ ID NO. 3):** 5' - TCC CGG GGC ACT CGC AAG
CAC CCT ATC AGG - 3'

Note: Those primers amplify a region of 256-nt present within the 5' untranslated
region of HCV.

10

PUTR Probe Sequence (SEQ ID NO. 4): 6FAM - TGG TCT GCG GAA CCG GTG
AGT ACA CC - TAMRA

- 15 **No Template Controls (NTC):** On each plate, 4 wells are used as "NTC". For these
controls, 5μl of water are added to the well in place of RNA.

Thermal Cycling Conditions:

50°C 2 min

60°C 30 min

95°C 5 min

20

95°C 15 sec } for 2 cycles

60°C 1 min

90°C 15 sec }
60°C 1 min } for 40 cycles

5

Following the termination of the RT-PCR reaction the data analysis requires setting of threshold fluorescence signal for the PCR plate and a standard curve was constructed by plotting the Ct value versus RNA copy number used in each reference reaction. The Ct values obtained for the assay samples are used to
10 interpolate an RNA copy number based on the standard curve.

Finally, the RNA copy number was normalized (based on the RiboGreen RNA quantification of the total RNA extracted from the cell culture well) and expressed as genome equivalents / µg of total RNA [ge/µg].

- 15 The RNA copy number [g.e./µg] from each well of the cell culture plate was a measure of the amount of replicating HCV RNA in the presence of various concentrations of inhibitor. The % inhibition was calculated with the following equation:

$$100 - [(g.e./\mu g \text{ inh}) / (g.e./\mu g \text{ ctrl}) \times 100].$$

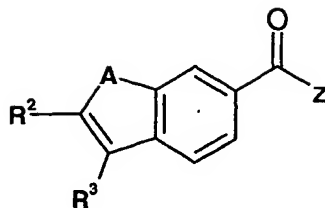
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A non-linear curve fit with the Hill model was applied to the inhibition-concentration data, and the 50% effective concentration (EC₅₀) was calculated by the use of SAS software (Statistical Software System; SAS Institute, Inc. Cary, N.C.).

- 25 In Tables 1 to 9 below, the following ranges apply:
IC₅₀: A = 10µM-1µM; B = 1µM-500nM; and C<500nM.
EC₅₀: A = 5µM-500nM; and B = ≤500nM

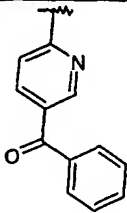
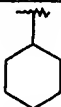
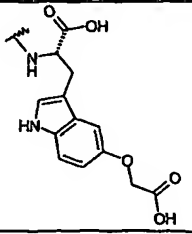
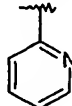
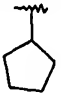
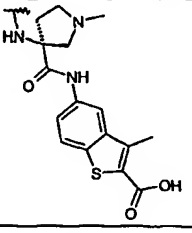
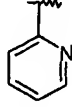

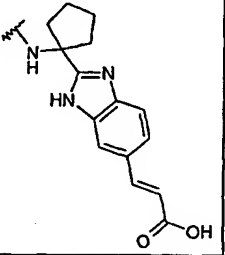
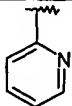
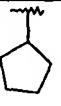
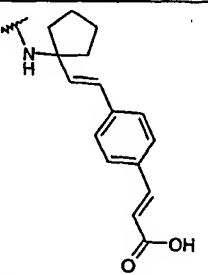
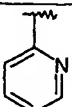
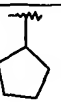
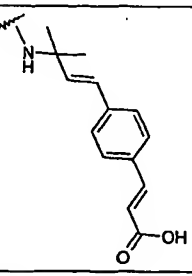
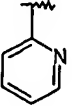
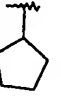
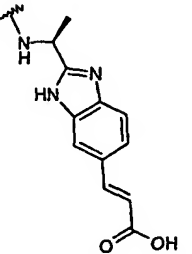
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TABLE 1

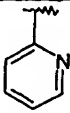

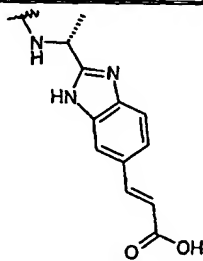
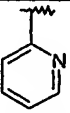
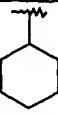
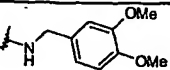
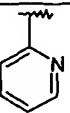

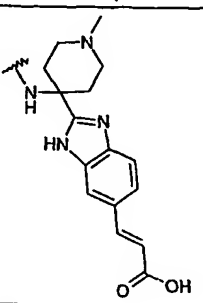
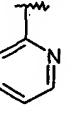

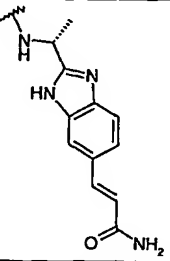


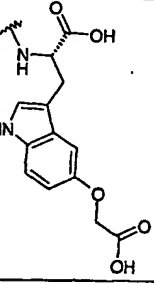
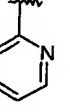

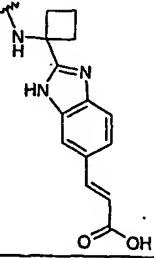


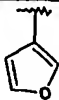
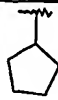
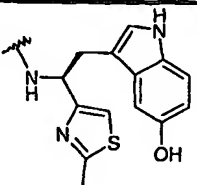
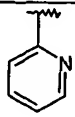
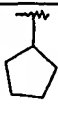
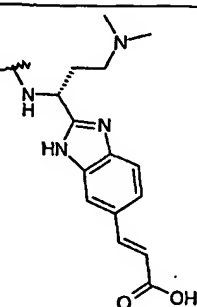
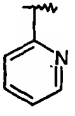
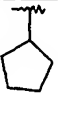
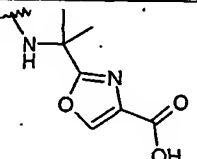
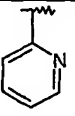
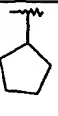
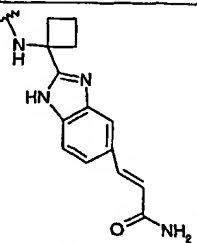
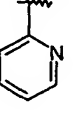

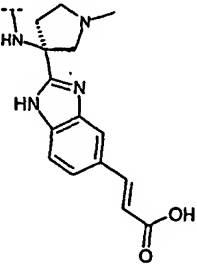
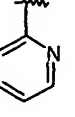
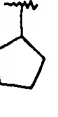
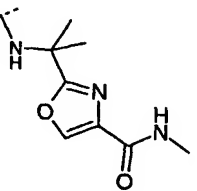
Cpd. #	A	R ²	R ³	Z	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
1001	NH				A	B	561.2
1002	NH				C	--	522.2
1003	NH				A	A	562.2
1004	NH				B	B	566.2
1005	NH				A	--	546.3

Cpd. #	A	R ²	R ³	Z	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
1006	NMe				C	B	648.3
1007					A	--	808.3
1008	NMe				B	--	815.3 (M-H)
1009	NMe				A	--	818.1
1010	NMe				C	--	636.3
1011	NMe				B	--	698.3

Cpd. #	A	R ²	R ³	Z	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
1012	NMe				C	--	699.3
1013	NMe				C	B	636.3
1014	NMe				C	B	574.4
1015	NMe				C	B	560.3
1016	NMe				C	B	534.2
1017	NMe				C	A	534.3

151

Cpd. #	A	R ²	R ³	Z	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
1018	NMe				C	B	534.3
1019	NH				A	--	470.3
1020	NMe				C	B	603.4
1021	NMe				C	B	533.4
1022	S				C	--	573.3
1023	NMe				C	C	560.4

Cpd. #	A	R ²	R ³	Z	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
1024	S				C	A	568.3
1025	NMe				C	A	591.4
1026	NMe				B	--	473.3
1027	NMe				C	B	559.4
1028	NMe				C	B	589.4
1029	NMe				B	--	486.4

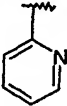

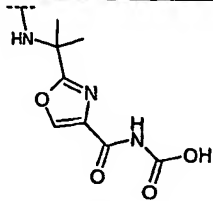
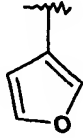

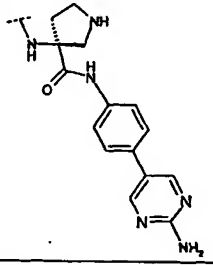
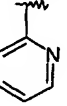
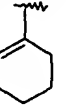
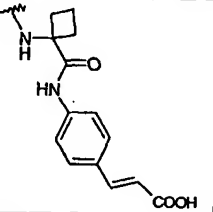
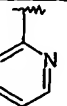

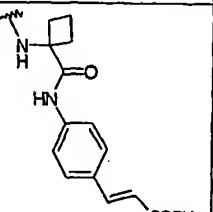
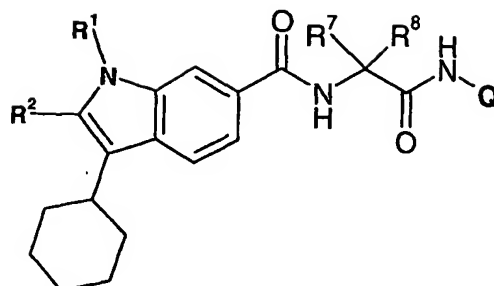


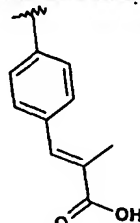


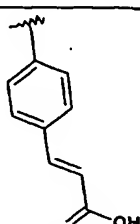

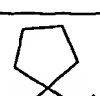
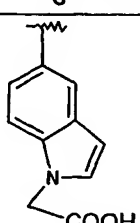

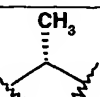
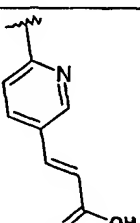

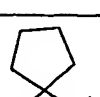
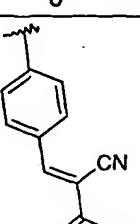

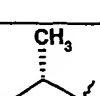
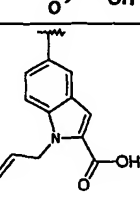

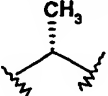
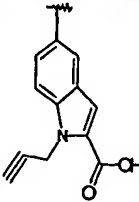


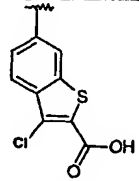

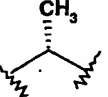
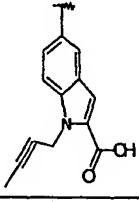

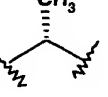
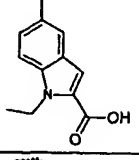


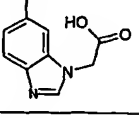


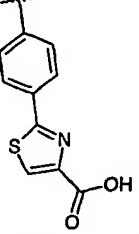


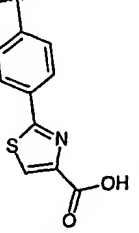
Cpd. #	A	R ²	R ³	Z	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
1030	NMe				B	--	530.4
1031	NMe				C	--	604.5
1032	NMe				C	C	575.5
1033	NMe				B		561.3




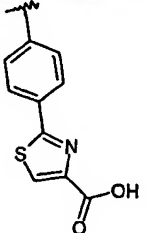


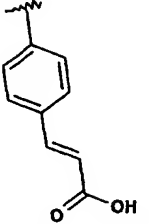



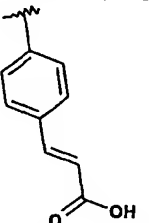



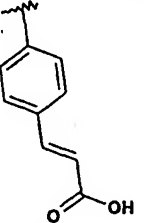

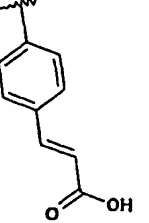
TABLE 2



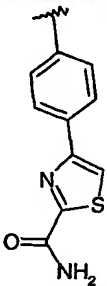

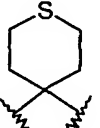
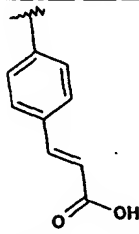
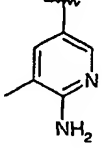

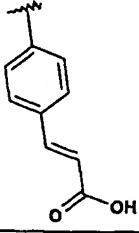
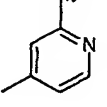

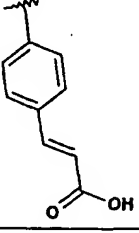
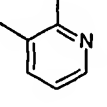

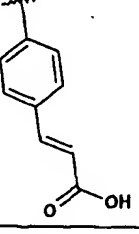
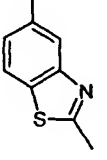

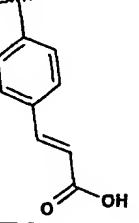


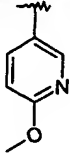

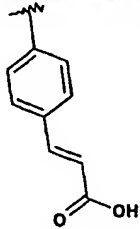
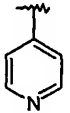

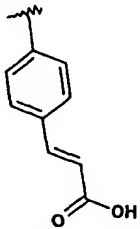
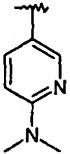

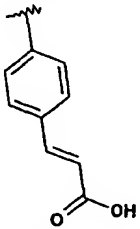
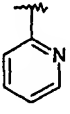
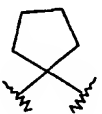
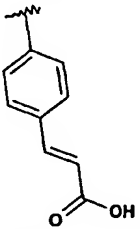
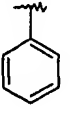

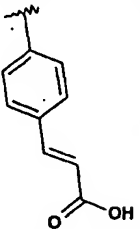
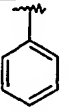
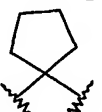
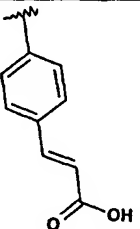
Cpd. #	R^1	R^2	R^7 R^8	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2001	H				B	B	534.2
2002	H				B	B	576.2
2003	H	Br			A	A	578.6 (MH ⁺)/ 580 (MH ⁺)
2004	H				B	B	526.2

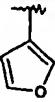

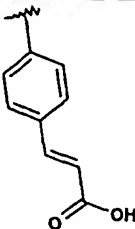


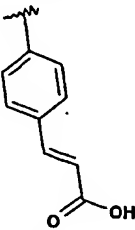


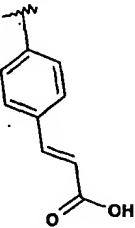
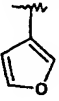

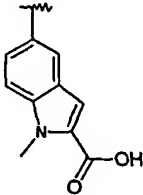
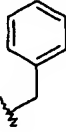
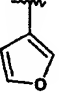

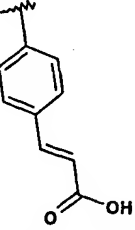
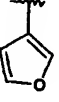
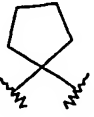
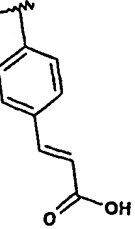
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2005	H				B	B	580.3
2006	Me				B	B	580.3
2008	H				B	A	593.2
2009	H				B	A	527.2
2010	H				B	A	589.3
2011	H				B	A	579.3



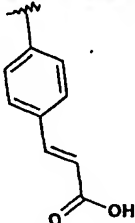
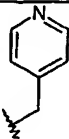
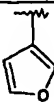

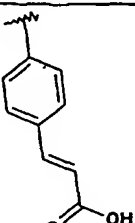
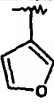

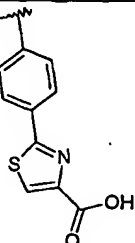
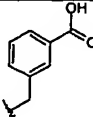
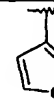
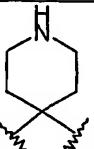
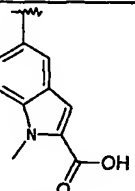
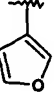

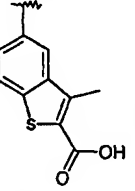


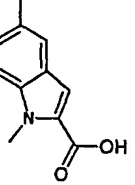
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2012	H				B	A	577.2
2013	H				B	B	630.2
2014	H				A	A	591.3
2015	H				B	B	567.2
2016	H				A	--	594.2
2017	H				B	B	597.2
2018	H				B	B	607.2

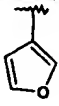

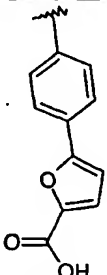
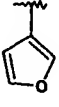
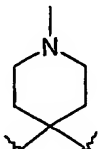
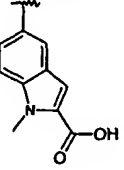
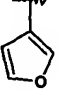

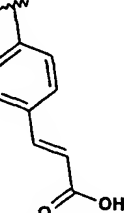
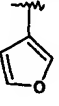

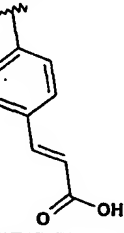

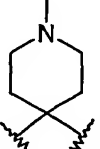
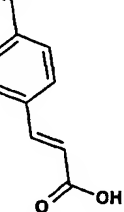
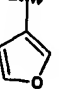

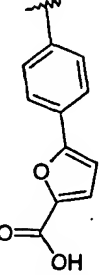
Cpd. #	R ¹	R ²		Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2019	H				B	A	613.1
2020	Et				B	B	578.2
2021					B	A	596.4
2022					A	--	592.3
2023	Me	H			A	--	488.2



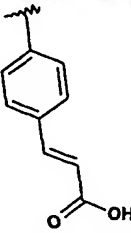
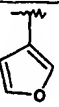
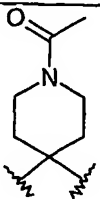
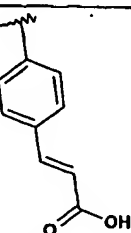
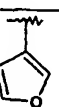
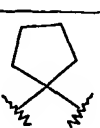
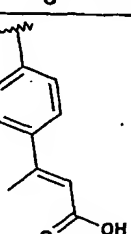
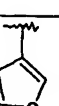

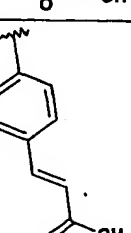
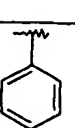
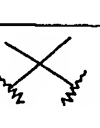
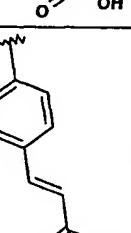
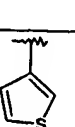

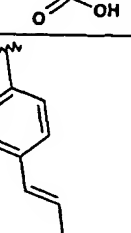
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2024	H				B	B	596.3
2025	H				B	B	596.3 (M-H)
2026	Me				B	--	594.4
2027	Me				B	--	579.3
2028	Me				A	--	579.3
2029	Me				B	--	635.3

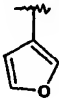

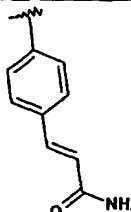
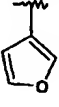

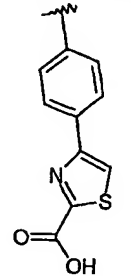
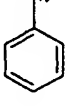

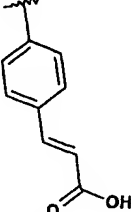
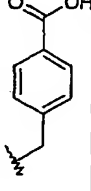
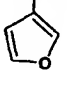

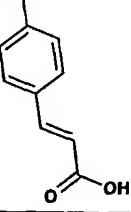

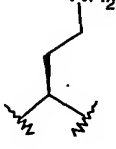
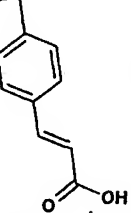
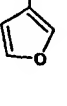
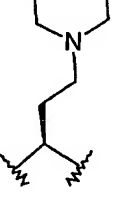
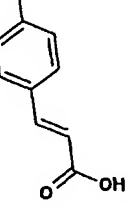
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2030	Me				C	B	565.3
2031	Me				C	B	595.3
2032	Me				B	B	608.4
2033	H				B	B	577.2
2034	Me				C	B	590.2
2035	H				C	B	576.2



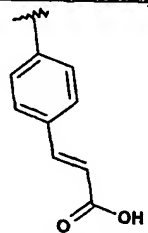

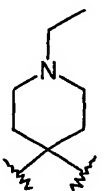
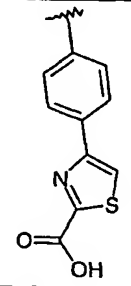


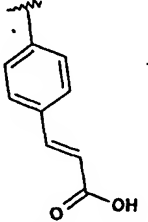

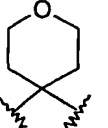
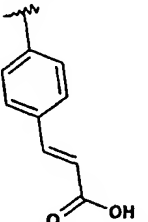
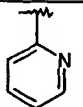

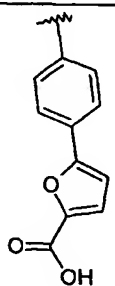
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2036	H				C	B	566.3
2037	H				C	B	566.2
2038	H				C	B	582.2
2039	H				C	B	593.3
2040					C	B	656.3
2041	Me				B	B	580.3

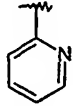

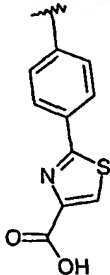
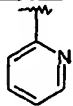

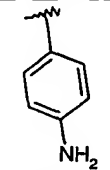
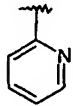

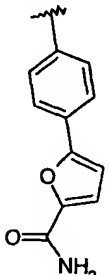
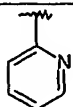

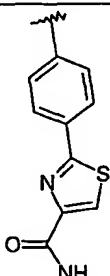
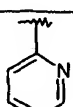

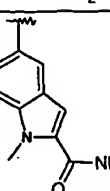
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2042	H				C	B	582.3
2043					C	B	657.3
2044	H				C	B	621.2
2045					C	--	742.3
2046	H				C	B	610.2
2047	H				C	B	553.2

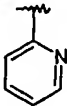

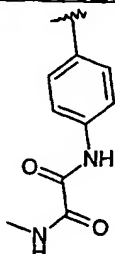
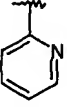

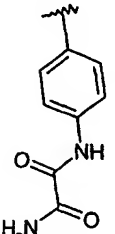
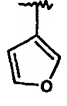
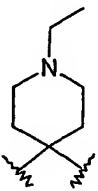
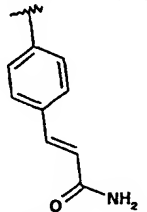
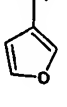
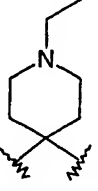
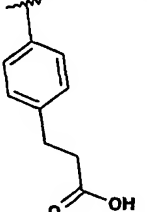
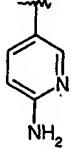

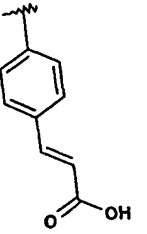
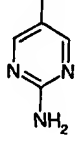

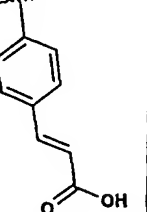
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2048	H				C	B	606.2
2049	H				C	A	620.3 (M-H)
2050	H				C	B	540.3
2051	Me				C	B	554.3
2052	H				C	B	595.4
2053	H				C	B	580.2

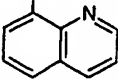

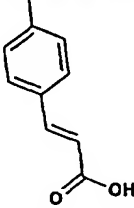

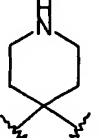
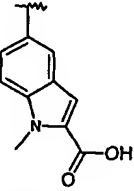

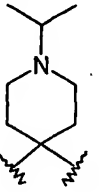
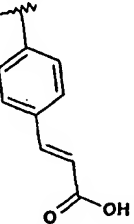
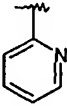

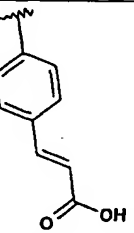

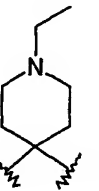
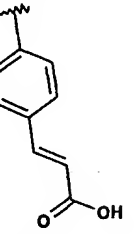
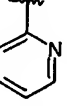

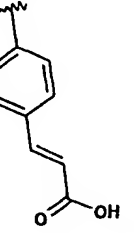
Cpd. #	R ¹	R ²	R⁷ R⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2054	Et				C	B	568.2
2055	H				C	B	623.2
2056	H				C	B	580.2
2057	H				C	B	552.2
2058	H				C	B	550.2
2059	H				C	B	556.2

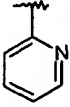

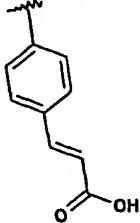
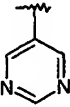

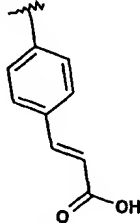
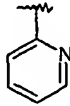
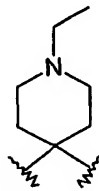
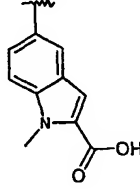
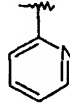

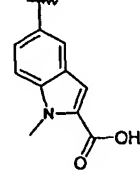
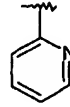

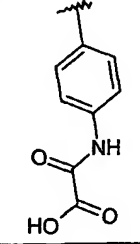
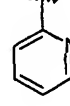

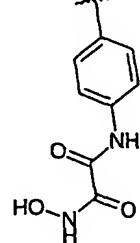
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2060	H				C	B	565.2
2061	H				C	A	597.1
2062	Me				C	B	564.2
2063					C	--	674.3
2064	H				C	--	555.2
2065	H				C	--	611.3

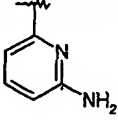

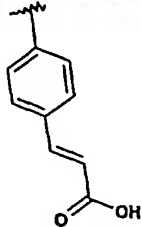
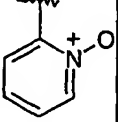

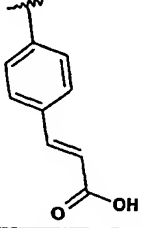
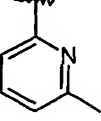

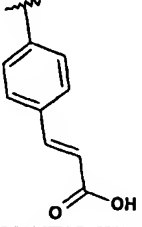
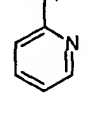
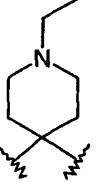
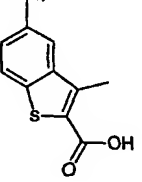
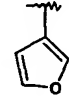
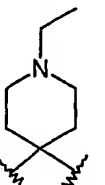
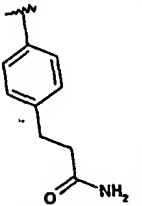
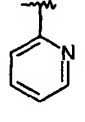
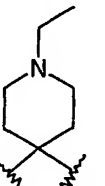
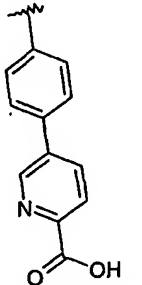
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2066	Me				C	B	570.2
2067	H				C	A	666.2
2068	Me				C	B	565.3
2069	H				C	B	582.3
2070	Me				C	B	605.2

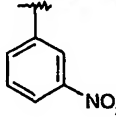

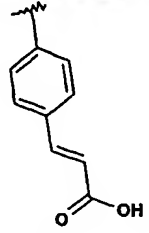
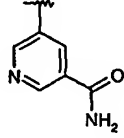

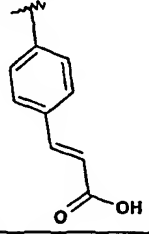
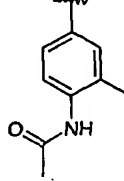

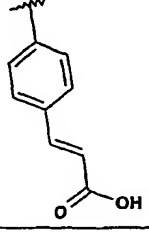

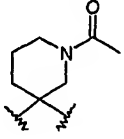
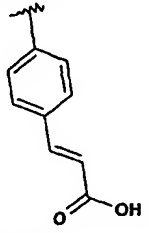

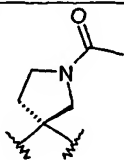
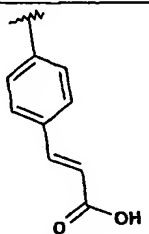


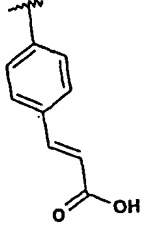
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2071	Me				C	B	622.2
2072	Me				C	B	510.2
2073	Me				C	B	604.2
2074	Me				C	B	621.2
2075	Me				C	B	591.3



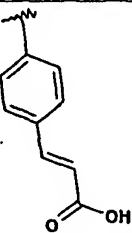
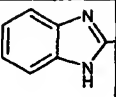

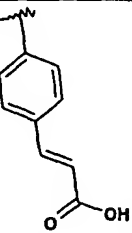
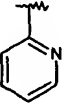
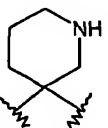
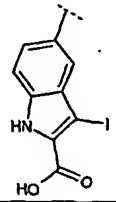
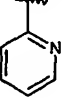

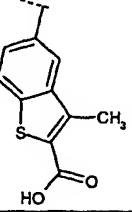
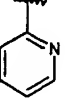

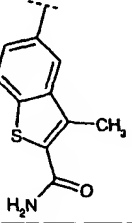
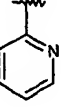

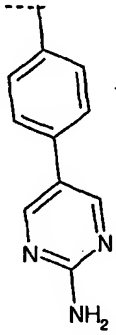
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2076	Me				C	B	595.3
2077	Me				C	B	581.3
2078	H				C	A	608.4
2079	H				C	A	611.4
2080	Me				C	B	580.3
2081	Me				C	B	581.3

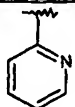
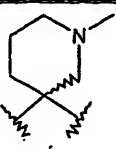
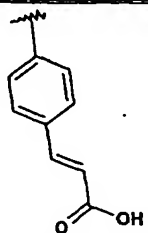
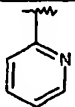
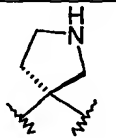
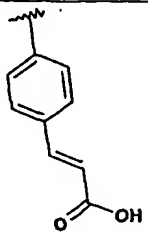
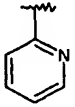

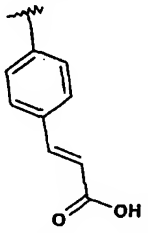
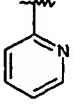

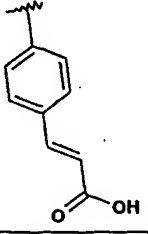
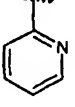

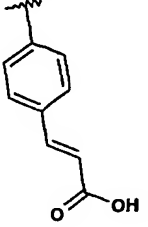
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2082	Me				C	B	615.3
2084	H				C	A	608.2
2086	H				C	B	623.3
2087	Me				C	B	565.2
2088	H				C	B	609.3
2089	H				C	B	551.2

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2090	Me				C	B	577.2
2091	Me				C	B	566.3
2092	Me				C	B	661.3
2093	Me				C	B	592.3
2094	Me				C	A	582.2
2095	Me				C	B	597.3

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2096	Me				C	B	580.3
2097	Me				C	A	581.3
2098	Me				C	B	579.3
2099	Me				C	B	678.4
2100	H				A	B	610.4
2101	Me				C	B	685.4

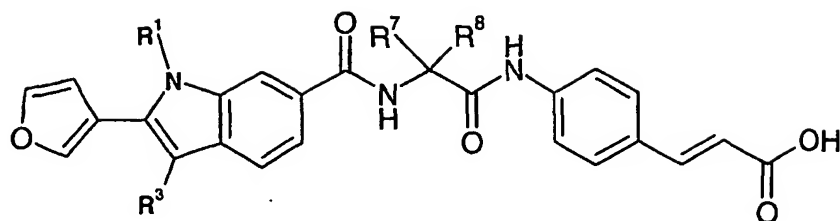
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2102	Me				C	B	609.3
2103	Me				C	B	608.3
2104	Me				C	B	635.4
2105	Me				C	B	648.3
2106	Me				C	B	634.3
2107	Me				C	B	648.2

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2108	Me				C	B	555.4
2109	Me				B	A	604.4
2110	Me				C	B	745.2
2111	Me				C	B	621.3
2112	Me				C	B	620.3
2113	Me				B	B	600.5

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
2114	Me				C	B	620.3
2115	Me				C	B	592.3
2116	Me				C	B	606.3
2117	Me				C	B	592.3
2118	Me				C	B	606

174

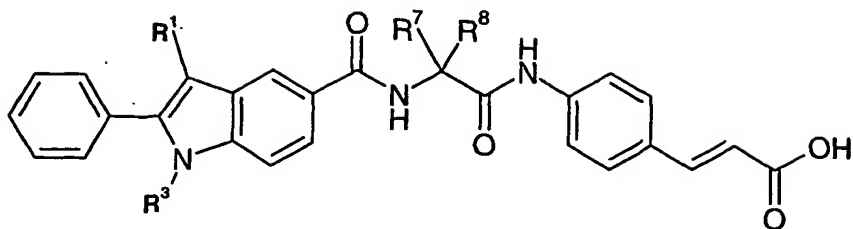
TABLE 3




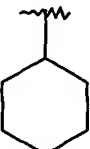



cpd. #	R ¹	R ³	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
3001	H			C	B	567.3
3002	H			C	B	552.2
3003	Me			C	B	526.2
3004	Me			C	C	538.3

175

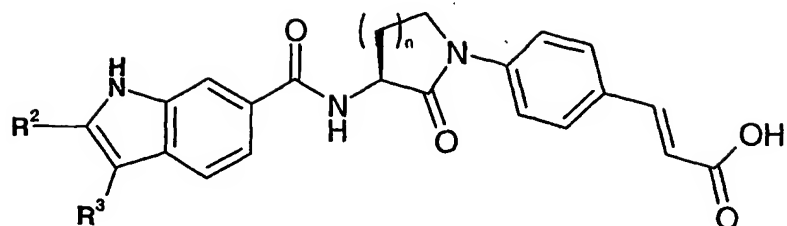
TABLE 4



cpd. #	R ¹	R ³		IC ₅₀	EC ₅₀	m/z (M+H) ⁺
4001	Me			B	B	590.3
4002	H			B	B	576.3

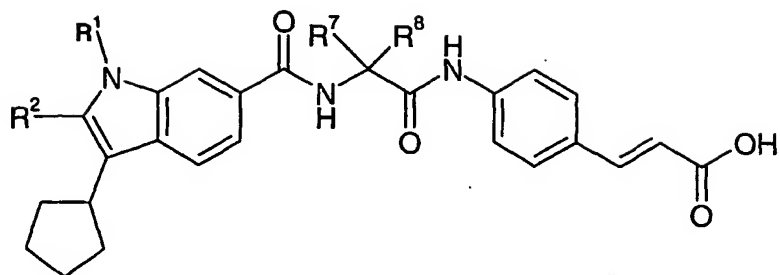
176

TABLE 5

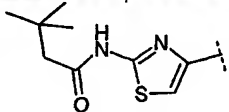
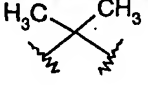
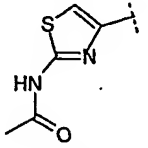
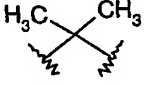
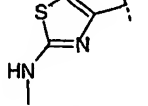

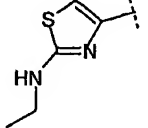
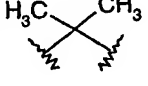
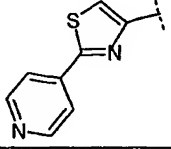

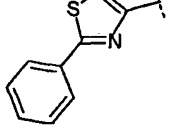

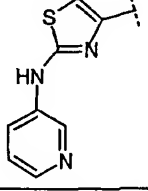

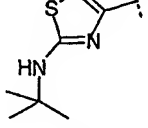

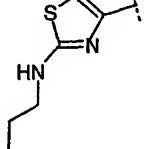




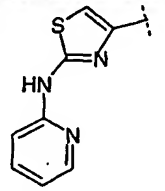
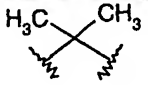
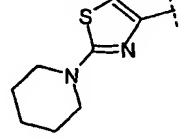
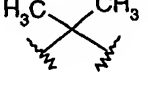
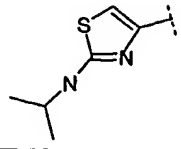
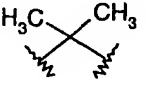
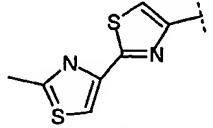
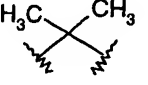
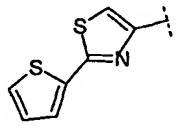
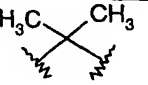
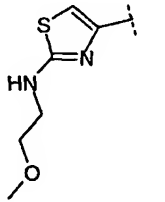
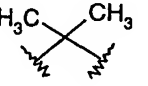
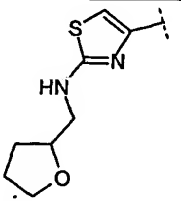
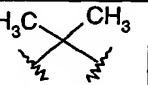
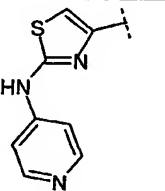
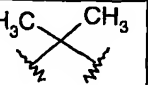
cpd. #	R ²	R ³	n	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
5001			1	A	--	538.2


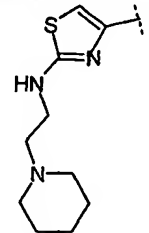
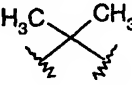
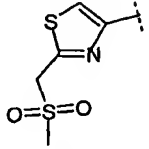
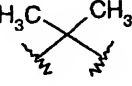
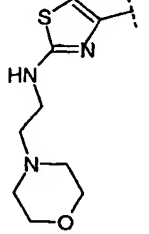
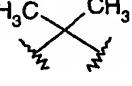
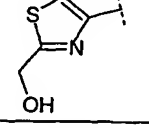
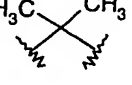
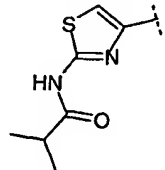
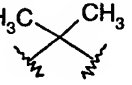
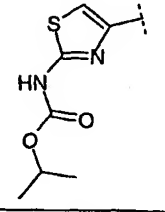
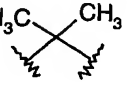
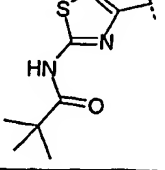
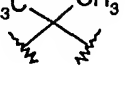
TABLE 6

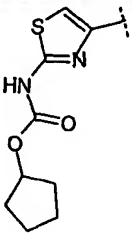
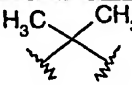
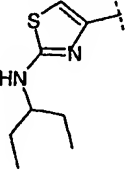
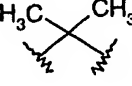
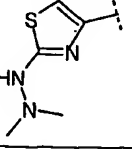
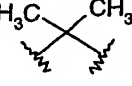
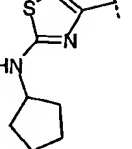

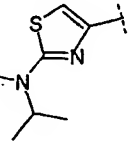
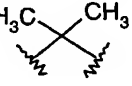
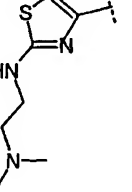

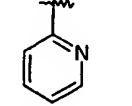

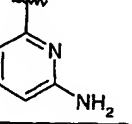



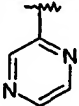
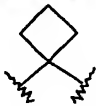
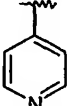

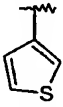

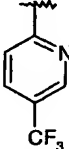

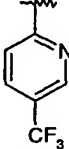
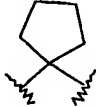
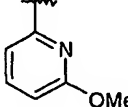

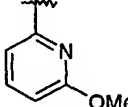
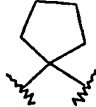
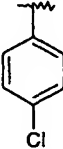



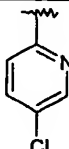

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6001	CH ₃			C	B	634.3
6002	CH ₃			C	B	634.3
6003	CH ₃			C	B	634.2
6004	CH ₃			B	--	648.2
6005	CH ₃			C	B	621.3
6006	CH ₃			C	B	633.3

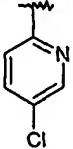

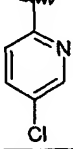

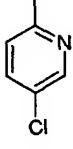
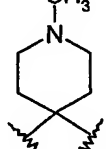
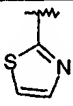

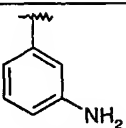
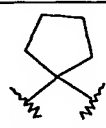
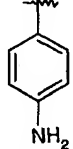

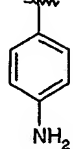
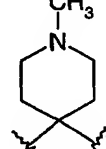
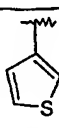

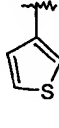
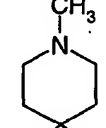
cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6007	CH ₃			C	B	670.3
6008	CH ₃			C	B	614.3
6009	CH ₃			C	B	586.3
6010	CH ₃			C	B	600.3
6011	CH ₃			C	B	634.3
6012	CH ₃			B	B	633.3
6013	CH ₃			C	B	649.3
6013	CH ₃			C	B	628.3
6014	CH ₃			C	B	614.3

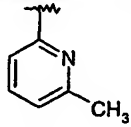
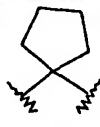
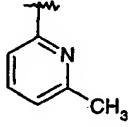
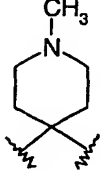
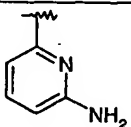
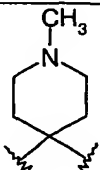
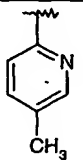

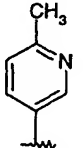
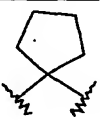
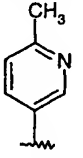
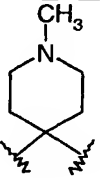
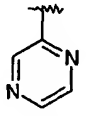
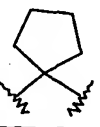
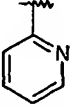

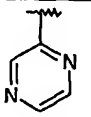
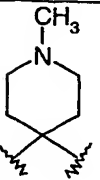
cpd. #	R ¹	R ²		IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6015	CH ₃			B	B	649.3
6016	CH ₃			C	B	640.4
6017	CH ₃			C	B	614.3
6018	CH ₃			C	B	654.3
6019	CH ₃			B	B	639.3
6020	CH ₃			C	B	630.3
6021	CH ₃			C	B	656.4
6022	CH ₃			B	B	649.3

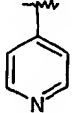
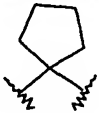
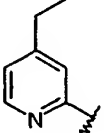
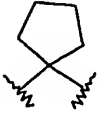
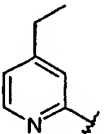
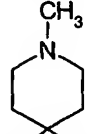
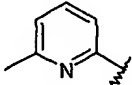



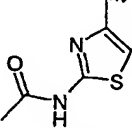

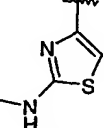

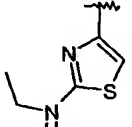

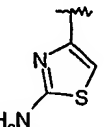

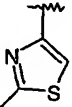
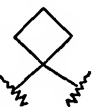
cpd. #	R ¹	R ²		IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6023	CH ₃			C	B	683.4
6024	CH ₃			C	B	649.3
6025	CH ₃			C	B	685.4
6026	CH ₃			C	B	587.3
6027	CH ₃			C	B	642.3
6028	CH ₃			C	B	658.3
6029	CH ₃			C	B	656.4

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6030	CH ₃			B	B	684.4
6031	CH ₃			B	B	642.4
6032	CH ₃			C	B	615.3
6033	CH ₃			B	B	640.4
6034	CH ₃			C	B	628.4
6035	CH ₃			C	B	643.4
6036	CH ₃			C	B	549.3
6037	CH ₃			C	B	564.3



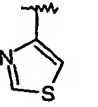

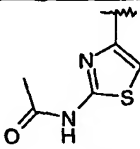

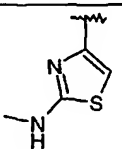

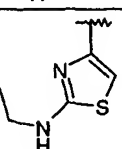

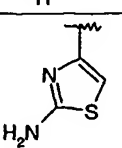
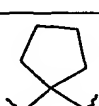
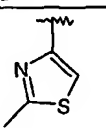

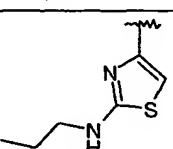

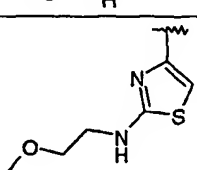
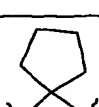
cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6038	CH ₃			C	B	564.3
6039	CH ₃			C	B	563.3
6040	CH ₃			C	B	568.3
6041	CH ₃			C	B	631.3
6042	CH ₃			C	B	645.3
6043	CH ₃			C	B	593.3
6044	CH ₃			C	B	607.3
6045	CH ₃			B	B	596.3
6046	CH ₃			C	B	500.2
6047	CH ₃			C	B	285.2

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6048	CH ₃			C	B	597/2
6049	CH ₃			C	B	611.2
6050	CH ₃			C	B	640.3
6051	CH ₃			C	B	583.3
6052	CH ₃			C	B	591.3
6053	CH ₃			C	B	591.3
6054	CH ₃			C	B	620.4
6055	CH ₃			C	B	582.3
6056	CH ₃			C	B	611.3

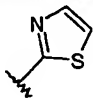
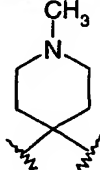
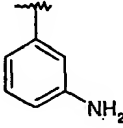
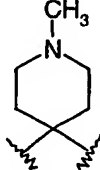
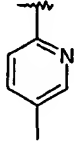
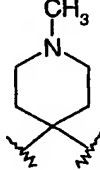
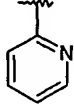
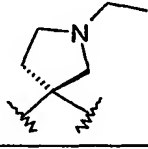
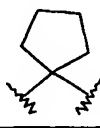
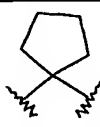
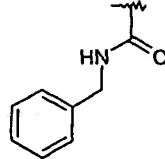

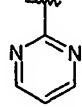

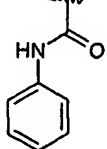

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6057	CH ₃			C	B	591.4
6058	CH ₃			C	B	620.4
6059	CH ₃			C	B	621.4
6060	CH ₃			C	B	591.4
6061	CH ₃			C	B	591.3
6062	CH ₃			C	B	620.4
6063	CH ₃			C	B	578.3
6064	CH ₃			C	B	563.3
6065	CH ₃			C	A	607.3

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6066	CH ₃			C	B	577.3
6067	CH ₃			A	A	605.4
6068	CH ₃			C	A	634.4
6069	CH ₃			C	B	577.3
6070	CH ₃			C	B	569.2
6071	CH ₃			C	B	626.2
6072	CH ₃			C	B	598.3
6073	CH ₃			C	B	612.3
6074	CH ₃			C	B	584.3
6075	CH ₃			C	B	583.3

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6076	CH ₃			C	B	626.3
6077	CH ₃			C	B	642.3
6078	CH ₃			C	B	695.4
6079	CH ₃			C	B	654.3
6080	CH ₃			C	B	682.4
6081	CH ₃			C	B	668.4
6082	CH ₃			C	B	655.4
6083	CH ₃			C	B	553.3

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6084	CH ₃			C	B	512.3
6085	CH ₃			C	B	583.3
6086	CH ₃			C	B	640.3
6087	CH ₃			C	B	612.3
6088	CH ₃			C	B	626.3
6089	CH ₃			C	B	598.3
6090	CH ₃			C	B	597.3
6091	CH ₃			C	B	640.4
6092	CH ₃			C	B	656.4

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6093	CH ₃			C	B	709.4
6094	CH ₃			C	B	668.4
6095	CH ₃			C	B	696.4
6096	CH ₃			C	B	682.4
6097	CH ₃			C	B	669.4
6098	CH ₃			C	B	567.3
6099	CH ₃			C	B	526.4
6100	CH ₃			C	B	541.3

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z. (M+H) ⁺
6101	CH ₃			C	B 0.165	612.3
6102	CH ₃			C	B	620.4
6103	CH ₃			C	B	620.4
6105	CH ₃			C	B	620.4
6106	CH ₃	CONHCH ₃		B	--	557.3
6107	CH ₃	CON(CH ₃) ₂		A	--	571.3
6110	CH ₃			A	--	633.3
6111	CH ₃			C	B	564.3
6112	CH ₃			B	-	593.3

cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6113	CH ₃	CONH ₂		B	--	517.3
6114	CH ₃			C	B	606.3
6115	CH ₃			C	B	606.3
6116	CH ₃			C	B	606.3
6117	CH ₃			C	B	607.3
6118	CH ₃			C	B	593.3
6119	CH ₃	H		A	--	486.3
6120	CH ₃	Br		B	--	566.2
6121	H			B	B	549.3
6122	CH ₃			C	B	581.3

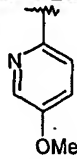

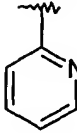
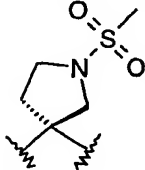
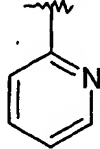
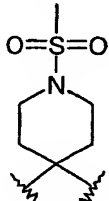
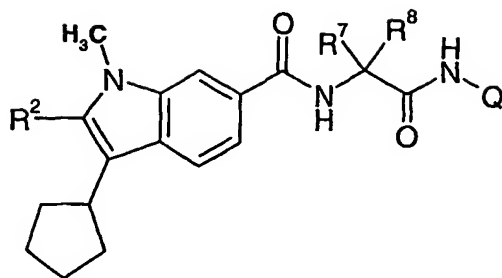



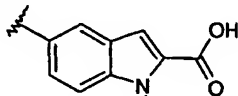


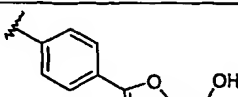


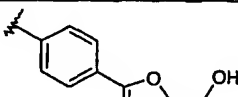


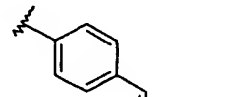


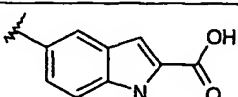
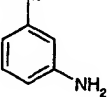

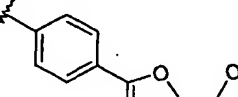
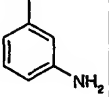

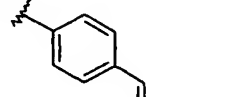
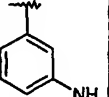

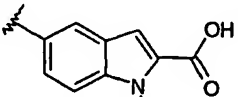


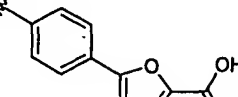
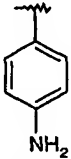
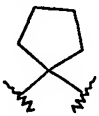
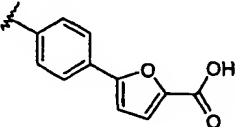
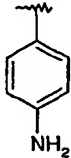

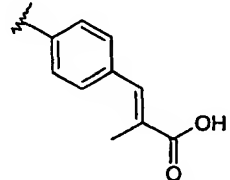
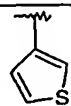

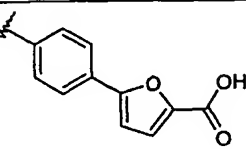
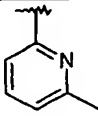
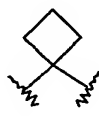
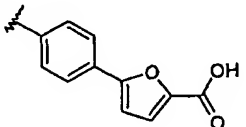
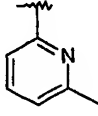
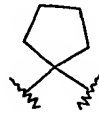
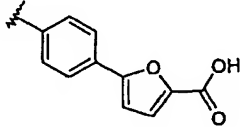
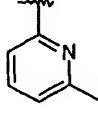

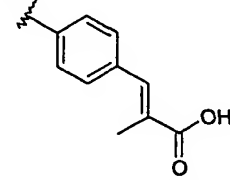
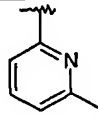
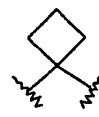
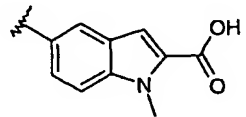
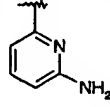

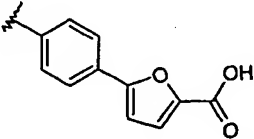
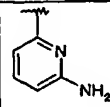

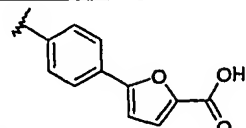
cpd. #	R ¹	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
6123	CH ₃			C	B	593.4
6124	CH ₃			C	B	656.4
6125	CH ₃			C	B	670.4

TABLE 7

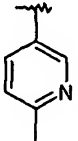

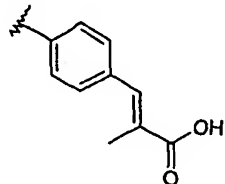
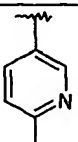

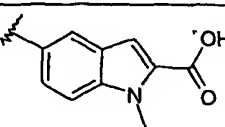
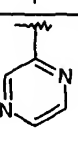

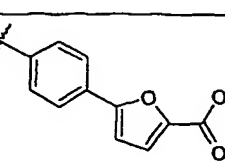
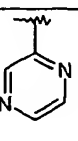

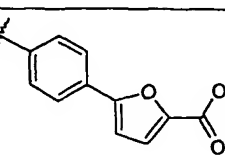
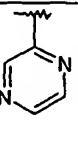

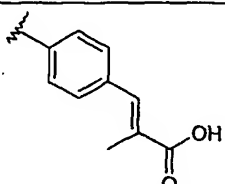
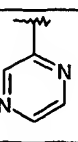

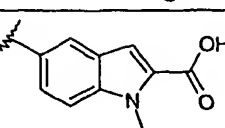
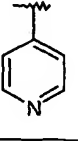

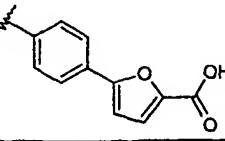
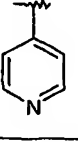

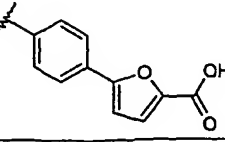
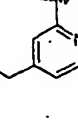

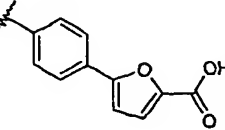


cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7001				C	B	577.3
7002				A	A	552.3
7003				A	A	551.3
7004				B	B	619.2
7005				C	B	577.3
7006				C	B	577.2
7007				C	B	627.2

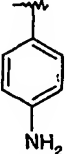

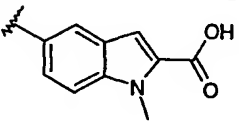
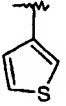

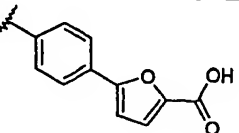
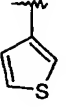

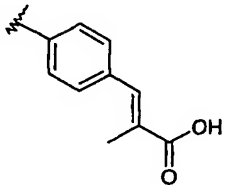
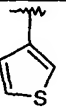
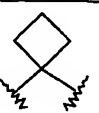
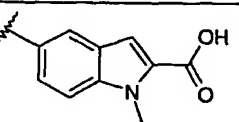
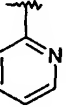

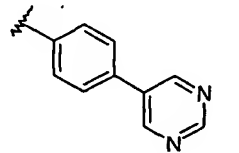
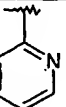

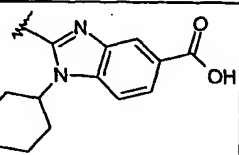
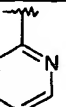

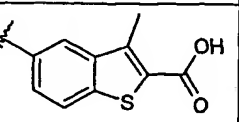
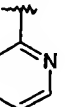

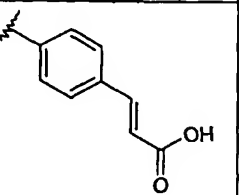
cpd #	R ²		Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7008				C	B	596.2
7009				C	B	603.3
7010				C	B	617.3
7011				C	B	577.3
7012				C	B	590.3
7013				C	B	631.3
7014				C	B	591.3
7015				C	B	604.3
7016				C	B	617.3

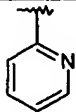

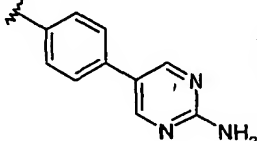
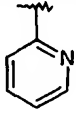
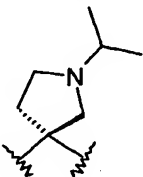
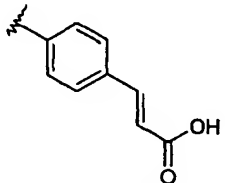
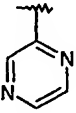

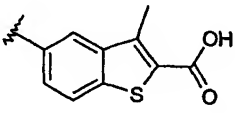
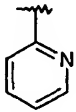

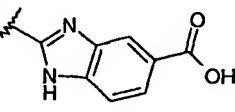
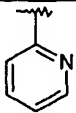

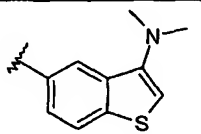
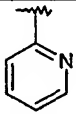

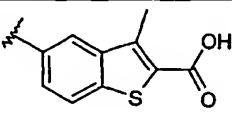
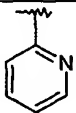

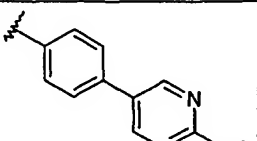
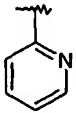

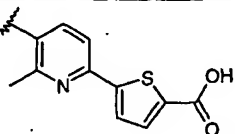
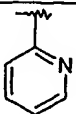
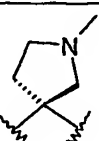
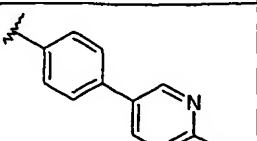
cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7017				C	B	631.3
7018				C	B	591.4
7019				C	B	608.3
7020				C	B	617.3
7021				C	B	631.3
7022				C	B	591.3
7023				C	B	604.4
7024				C	B	618.3
7025				C	B	632.3

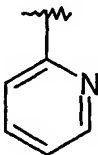

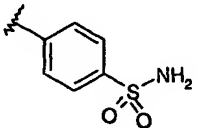
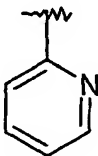

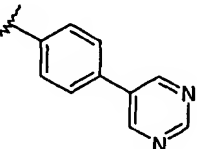
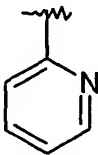

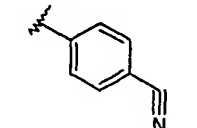
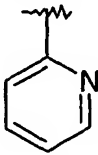

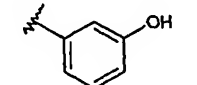
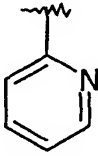

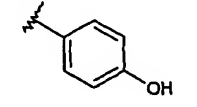
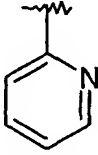

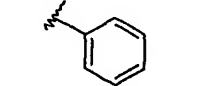
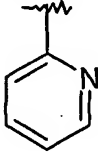

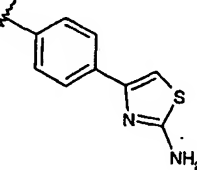
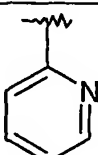

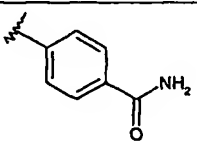
cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7026				C	B	592.3
7027				C	B	605.3
7028				C	B	617.3
7029				C	B	631.3
7030				C	B	591.4
7031				C	B	604.3
7032				C	B	617.3
7033				C	B	631.4

cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7034				C	B	591.4
7035				C	B	604.3
7036				C	B	604.3
7037				C	B	618.3
7038				C	B	578.3
7039				C	B	613.3
7040				C	B	603.3
7041				C	B	617.3
7042				A	A	631.3

cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7043				A	A	645.4
7044				A	A	605.4
7045				A	A	618.4
7046				C	--	650.2
7047				C	B	609.3
7048				C	B	623.3
7049				C	B	583.3
7050				C	B	617.4

cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7051				C	B	604.4
7052				C	B	622.3
7053				C	B	582.3
7054				C	B	595.3
7055				B	A	571.3
7056				A	--	647.4
7057				C	B	636.3
7058				C	B	592.4

cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7059				C	A	601.4
7060				C	B	620.5
7061				C	B	637.3
7062				C	--	577.4
7063				B	--	592.4
7064				C	B	607.3
7065				B	A	586.4
7066				A	A	634.4
7067				C	--	615.4

cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7068				C	B	572.4
7069				C	B	600.4
7070				B	--	518.4
7071				C	--	509.3
7072				C	--	509.4
7073				B	--	493.4
7075				C	--	620.5
7076				C		536.4

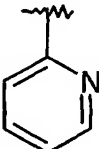

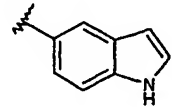
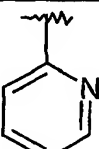

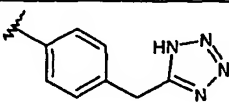
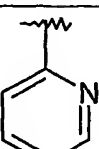

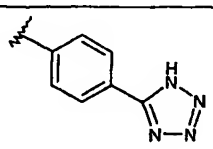
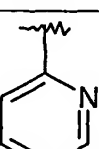

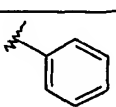
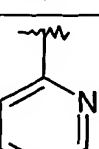
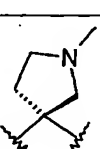
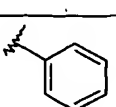
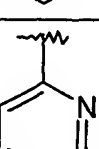
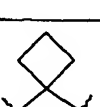
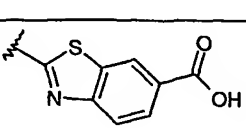
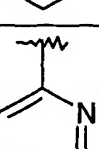
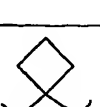
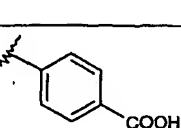
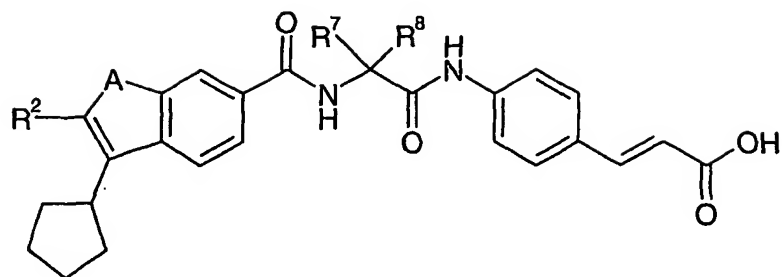
cpd #	R ²	R ⁷ R ⁸	Q	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
7077				C	B	532.4
7078				B	--	575.3
7079				C	B	561.3
7080				C	A	508.5
7081				C	A	522.3
7082				C	--	594.2
7083				C	--	537.3

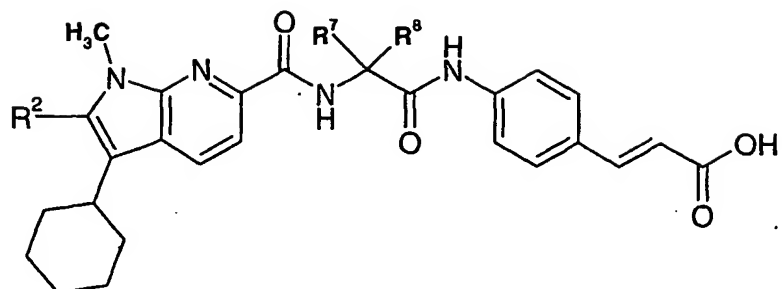
TABLE 8



cpd. #	A	R ²	R ⁷ R ⁸	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
8001	S			A	A	566.3
8002	S			A	A	554.3
8003	S			B	--	555.3
8004	S			C	--	543.3
8005	O			A	--	550.3
8006	O			A	--	538.3

203

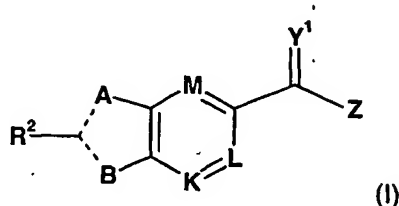
TABLE 9



cpd. #	R^2	R^7 R^8	IC ₅₀	EC ₅₀	m/z (M+H) ⁺
9001			B	—	591.4
9002			C	B	567.4

CLAIMS

1. An isomer, enantiomer, diastereoisomer, or tautomer of a compound, represented by formula I:



wherein:

- 5 **A** is O, S, NR¹, or CR¹, wherein R¹ is selected from the group consisting of: H, (C₁₋₆)alkyl optionally substituted with:
 -halogen, OR¹¹, SR¹¹ or N(R¹²)₂, wherein R¹¹ and each R¹² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het, said aryl or Het optionally substituted with R¹⁰; or
 10 both R¹² are covalently bonded together and to the nitrogen to which they are both attached to form a 5, 6 or 7-membered saturated heterocycle;
- represents either a single or a double bond;
- 15 R² is selected from: halogen, R²¹, OR²¹, SR²¹, COOR²¹, SO₂N(R²²)₂, N(R²²)₂, CON(R²²)₂, NR²²C(O)R²² or NR²²C(O)NR²² wherein R²¹ and each R²² is independently H, (C₁₋₆)alkyl, haloalkyl, (C₂₋₆)alkenyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkynyl, (C₅₋₇)cycloalkenyl, 6 or 10-membered aryl or Het, said R²¹ and R²² being optionally substituted with R²⁰;
 20 or both R²² are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;
- B** is NR³ or CR³, with the proviso that one of **A** or **B** is either CR¹ or CR³, wherein R³ is selected from (C₁₋₆)alkyl, haloalkyl, (C₃₋₇)cycloalkyl, (C₅₋₇)cycloalkenyl, (C₆₋₁₀)bicycloalkyl, (C₆₋₁₀)bicycloalkenyl, 6- or 10-membered aryl, Het, (C₁₋₆)alkyl-aryl
 25 or (C₁₋₆)alkyl-Het,
 said alkyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, Het, alkyl-aryl and alkyl-Het being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C₁₋₆)alkyl optionally substituted with:

- OR³¹ or SR³¹ wherein R³¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het; or

5 - N(R³²)₂ wherein each R³² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het; or both R³² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

10 b) OR³³ wherein R³³ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het;

c) SR³⁴ wherein R³⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het; and

15 d) N(R³⁵)₂ wherein each R³⁵ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het; or both R³⁵ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

20

K is N or CR⁴, wherein R⁴ is H, halogen, (C₁₋₆)alkyl, haloalkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or R⁴ is OR⁴¹ or SR⁴¹, COR⁴¹ or NR⁴¹COR⁴¹ wherein each R⁴¹ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl;

25 or R⁴ is NR⁴²R⁴³ wherein R⁴² and R⁴³ are each independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, or both R⁴² and R⁴³ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

L is N or CR⁵, wherein R⁵ has the same definition as R⁴ defined above;

30

M is N or CR⁷, wherein R⁷ has the same definition as R⁴ defined above;

Y¹ is O or S;

Z is OR^6 wherein R^6 is C_{1-6} alkyl substituted with:

- 1 to 4 substituents selected from: OPO_3H , NO_2 , cyano, azido, $\text{C}(=\text{NH})\text{NH}_2$, $\text{C}(=\text{NH})\text{NH}(\text{C}_{1-6})\text{alkyl}$ or $\text{C}(=\text{NH})\text{NHCO}(\text{C}_{1-6})\text{alkyl}$; or

- 1 to 4 substituents selected from:

- 5 **a)** (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-8}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} ;
- 10 **b)** OR^{104} wherein R^{104} is (C_{1-6}) alkyl substituted with R^{150} , (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;
- 15 **c)** OCOR^{105} wherein R^{105} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;
- 20 **d)** SR^{108} , SO_3H , $\text{SO}_2\text{N}(\text{R}^{108})_2$ or $\text{SO}_2\text{N}(\text{R}^{108})\text{C}(\text{O})\text{R}^{108}$ wherein each R^{108} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** or heterocycle being optionally substituted with R^{150} ;
- 25 **e)** $\text{NR}^{111}\text{R}^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)**Het**, COOR^{115} or $\text{SO}_2\text{R}^{115}$ wherein R^{115} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)**Het**, or heterocycle being optionally substituted with R^{150} ;
- 30 **f)** $\text{NR}^{116}\text{COR}^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or

(C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁵⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰, or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

j) COOR¹²⁸ wherein R¹²⁸ is (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R¹⁵⁰, wherein R¹⁵⁰ is selected from:

208

- 1 to 3 substituents selected from: halogen, NO₂, cyano, azido or

- 1 to 3 substituents selected from:

- 5 **a)** (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;
- b)** OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;
- 10 **c)** OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 15 **d)** SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**; (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or
- 20 heterocycle being optionally substituted with R¹⁶⁰;
- e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵
- 25 is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle
- 30 being optionally substituted with R¹⁶⁰;
- f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted

with R^{160} ;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R^{160} ;

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C₁₋₆)alkyl optionally substituted with R^{160} , and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R^{124} is OH or O(C₁₋₆alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R^{160} ;

i) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R^{160} ; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R^{160} ;

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, $COOR^{161}$, SO_3H , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$, or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to

210

which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or Z is OR⁶ wherein R⁶ is (C₁₋₆alkyl)aryl substituted with:

- 5 - 1 to 4 substituents selected from: OPO₃H, azido, C(=NH)NH₂,
C(=NH)NH(C₁₋₆)alkyl or C(=NH)NHCO(C₁₋₆)alkyl; or
- 1 to 4 substituents selected from:
- 10 a) (C₁₋₆)alkyl substituted with R^{150a}, haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇
spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋
8)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl,
alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R¹⁵⁰,
wherein R^{150a} is the same as R¹⁵⁰ but is not COOR^{150b}, N(R^{150b})₂,
NR^{150b}C(O)R^{150b}, OR^{150b}, SR^{150b}, SO₂R^{150b}, SO₂N(R^{150b})₂, wherein R^{150b} is H
or unsubstituted C₁₋₆alkyl;
- 15 b) OR¹⁰⁴ wherein R¹⁰⁴ is (C₁₋₆alkyl) substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or
(C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said
cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally
substituted with R¹⁵⁰;
- 20 c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋
7)cycloalkyl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl,
Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- 25 d) SR^{108a}, SO₂N(R^{108a})₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is
independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl,
Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R¹⁰⁸ are covalently bonded
together and to the nitrogen to which they are attached to form a 5, 6 or 7-
membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋
6alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with
R¹⁵⁰, wherein R^{108a} is the same as R¹⁰⁸ but is not H or unsubstituted C₁₋₆alkyl;
- 30 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋
7)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R¹¹² is H, CN, (C₁₋
6alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl,
(C₁₋₆alkyl)Het, provided that when R¹¹¹ is H or unsubstituted alkyl, R¹¹² is not
H or unsubstituted alkyl, or R¹¹² is also COOR¹¹⁵ or SO₂R^{115a} wherein R¹¹⁵ is
H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋

- alkyl)aryl or (C₁₋₆alkyl)Het, and R^{115a} is the same as R¹¹⁵ but is not H or unsubstituted alkyl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R¹⁵⁰;
- 5 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- 10 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H; (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁵⁰;
- 15 h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;
- 20 i) COR¹²⁷ wherein R¹²⁷ is (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- 25 j) COOR¹²⁸ wherein R¹²⁸ is (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋
- 30

₆alkyl)Het being optionally substituted with R^{150} ;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R^{150} ;

l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R^{150} , wherein R^{150} is:

- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R^{160} ;

b) OR^{104} wherein R^{104} is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R^{160} ;

c) $OCOR^{105}$ wherein R^{105} is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R^{150} ;

d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R^{160} ;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R^{112} is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl,

aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;

f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁶⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl optionally substituted with R¹⁶⁰; and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁶⁰;

i) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰; and

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋

- alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁶⁰;
- wherein, R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and R¹⁶² are as defined above;
- or Z is OR⁶ wherein R⁶ is, (C₃₋₆)cycloalkyl, (C₂₋₆)alkenyl, 6- or 10-membered aryl, Het, (C₁₋₆)alkyl-Het, wherein said cycloalkyl, alkenyl, aryl, Het or alkyl-Het, is optionally substituted with R⁶⁰;
- or Z is N(R^{6a})R⁶, wherein R^{6a} is H or (C₁₋₆alkyl) and R⁶ is (C₁₋₆)alkyl optionally substituted with:
- 1 to 4 substituents selected from: OPO₃H, NO₂, cyano, azido, C(=NH)NH₂, C(=NH)NH(C₁₋₆)alkyl or C(=NH)NHCO(C₁₋₆)alkyl; or
 - 1 to 4 substituents selected from:
- a) (C₁₋₆) alkyl substituted with R^{150a}, haloalkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰, wherein R^{150a} is the same as R¹⁵⁰ but is not halogen, OH, O(C₁₋₆alkyl), COOH, COO(C₁₋₆alkyl), NH₂, NH(C₁₋₆alkyl) and N(C₁₋₆alkyl)₂;
- b) OR¹⁰⁴ wherein R¹⁰⁴ is (C₁₋₆alkyl) substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- d) SR¹⁰⁸, SO₃H, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R¹⁰⁸ are covalently bonded

215

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;

- 5 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**,
 10 provided that when R¹¹¹ is H or unsubstituted alkyl, R¹¹² is not H or unsubstituted alkyl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 15 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 20 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said
 25 alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 30 **h)** NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated

heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

j) COOR¹²⁸ wherein R¹²⁸ is (C₁₋₆)alkyl substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰, wherein R¹⁵⁰ is selected from:

- 1 to 3 substituents selected from: halogen, NO₂, cyano, azido or
- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are

attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

- 5 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;
- 10 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;
- 15 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;
- 20 **h)** NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl optionally substituted with R¹⁶⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;
- 25 **i)** tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl,
- 30

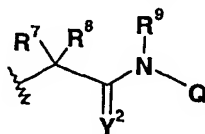
or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**,
said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**,
(C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰,
and

5 **k)** CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl,
10 cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰,

wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from:
tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H,
SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or
15 CON(R¹⁶²)₂, wherein R¹⁶¹ and R¹⁶² are as defined above;

or Z is N(R^{6a})R⁶ wherein R^{6a} is as defined above and R⁶ is (C₃₋₆)cycloalkyl,
(C₂₋₆)alkenyl, 6- or 10-membered aryl, **Het**, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-**Het**, wherein
said alkyl, cycloalkyl, alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally
20 substituted with R⁶⁰;

or Z is OR⁶ or N(R^{6a})R⁶ wherein R^{6a} is as defined above and R⁶ is:



wherein R⁷ and R⁸ are each independently H, (C₁₋₆)alkyl, haloalkyl, (C₃₋₇)cycloalkyl, 6-
25 or 10-membered aryl, **Het**, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-**Het**, wherein said alkyl,
cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-**Het** are optionally substituted with R⁷⁰;
or

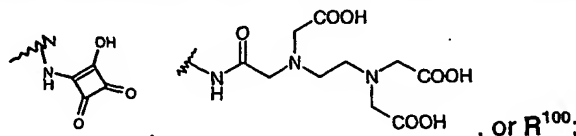
R⁷ and R⁸ are covalently bonded together to form second (C₃₋₇)cycloalkyl or a 4, 5- or
6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S;
30 or when Z is N(R^{6a})R⁶, either of R⁷ or R⁸ is covalently bonded to R^{6a} to form a
nitrogen-containing 5- or 6-membered heterocycle;

Y^2 is O or S;

R^9 is H, (C₁₋₆ alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-**Het**, all of which optionally substituted with R^{90} ; or

5 R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle;

Q is a 6- or 10-membered aryl, **Het**, (C₁₋₆) alkyl-aryl, (C₁₋₆) alkyl-**Het**, (C₁₋₆) alkyl-CONH-aryl or (C₁₋₆) alkyl-CONH-**Het**, all of which being optionally substituted with:



10 or a salt or a derivative thereof;

wherein **Het** is defined as 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicyclic having 1 to 5 heteroatoms selected from O, N and S; and

15

R^{10} , R^{20} , R^{60} , R^{70} , R^{90} and R^{100} is each defined as:

- 1 to 4 substituents selected from: halogen, OPO_3H , NO_2 , cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})alkyl$ or $C(=NH)NHCO(C_{1-6})alkyl$; or
- 1 to 4 substituents selected from:

- 20 a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R^{150} ;
- b) OR^{104} wherein R^{104} is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R^{150} ;
- 25 c) $OCOR^{105}$ wherein R^{105} is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R^{150} ;
- 30 d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or both R^{108} are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰,

- 5 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 10 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 15 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- 20 h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 25 or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or
- 30

(C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

5 j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

10 k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;

15 l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R¹⁵⁰, wherein R¹⁵⁰ is defined as:

- 1 to 3 substituents selected from: halogen, OPO₃H, NO₂, cyano, azido, C(=NH)NH₂, C(=NH)NH(C₁₋₆alkyl) or C(=NH)NHCO(C₁₋₆alkyl); or

20 - 1 to 3 substituents selected from:

a) (C₁₋₆)alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

25 b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

30 c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R¹⁰⁸ are

covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

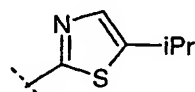
5 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;

15 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

20 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

25 **h)** NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰, or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋

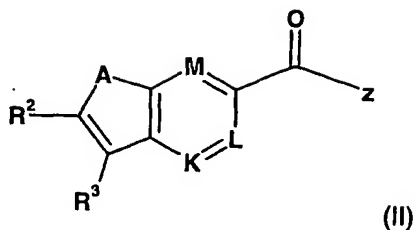
- 7)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁶⁰;
- 5 i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;
- 10 j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰; and
- 15 k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁶⁰; and
- 20 wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SR¹⁶¹, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both R¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,
- 30 or a salt thereof,
- with the proviso that, when A is CH, R² is phenyl or N-butyl, B is NR³, R³ is Me, K is



CH, L is CH, M is CH, Y¹ is O, and Z is NHR⁶, then R⁶ is not

224

2. A compound of formula (II):



wherein, A is O, S, or NR¹ and R¹, R², R³, K, L, M and Z are as defined in claim 1.

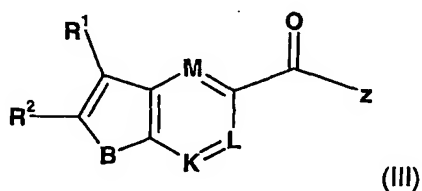
3. The compound according to claim 2, wherein A is NR¹.

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4. The compound according to claim 2, wherein M, K and L is CH or N.

5. The compound according to claim 4, wherein M, K and L is CH.

6. A compound of formula (III):



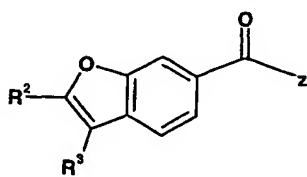
wherein, B is NR³ and R¹, R², R³, K, L, M and Z are as defined in claim 1.

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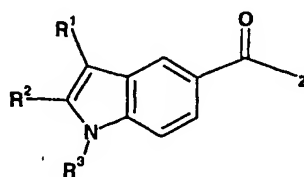
7. The compound according to claim 6, wherein M, K and L is CH or N.

8. The compound according to claim 7, wherein M, K and L is CH.

9. A compound of the formula:

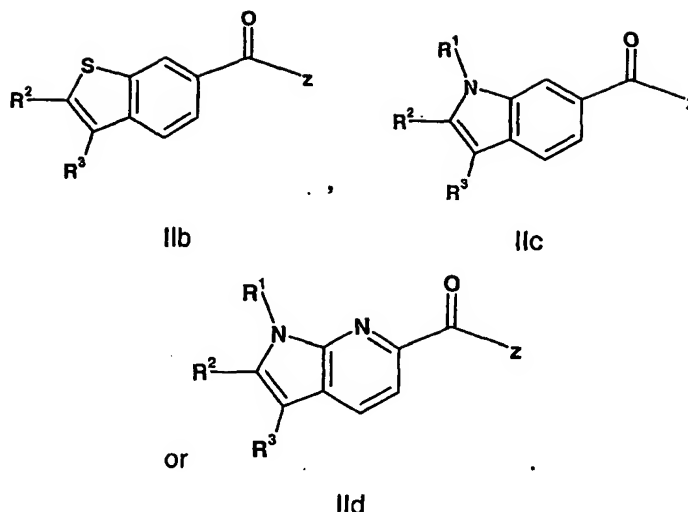


IIa



IIIa

225



5 wherein R^1 , R^2 , R^3 and Z are as defined in claim 1.

10. The compound according to claim 1, wherein R^1 is selected from: H or (C_{1-6}) alkyl.

11. The compound according to claim 10, wherein R^1 is H, CH_3 , isopropyl, or isobutyl.

12. The compound according to claim 11, wherein R^1 is H or CH_3 .

13. The compound according to claim 12, wherein R^1 is CH_3 .

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14. The compound according to claim 1, wherein R^2 is $CON(R^{22})_2$, wherein each R^{22} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{5-7}) cycloalkenyl, 6 or 10-membered aryl or Het, or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached; or R^2 is selected from: H, halogen, (C_{1-6}) alkyl, haloalkyl, (C_{2-6}) alkenyl, (C_{5-7}) cycloalkenyl, 6 or 10-membered aryl or Het; wherein each of said alkyl, haloalkyl, (C_{2-6}) alkenyl, (C_{5-7}) cycloalkenyl, aryl or Het is optionally substituted with R^{20} , wherein R^{20} is defined as:

- 15
- 1 to 4 substituents selected from: halogen, NO_2 , cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$ alkyl or $C(=NH)NHCO(C_{1-6})$ alkyl; or
 - 1 to 4 substituents selected from:

- a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰;
- b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁵⁰;
- c) OCOR¹⁰⁵ wherein R¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁵⁰;
- d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or heterocycle being optionally substituted with R¹⁵⁰;
- e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or heterocycle being optionally substituted with R¹⁵⁰;
- f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁵⁰;
- g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which

they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;

5 h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

10 i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

15 j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

20 k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

25 l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰; wherein R¹⁵⁰ is:

- 30 - 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, said alkyl or cycloalkyl optionally substituted with R¹⁶⁰;

- d) SR^{108} , SO_3H , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het and heterocycle being optionally substituted with R^{160} ;
- e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, or (C_{3-7}) cycloalkyl, and R^{112} is H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160} ;
- f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl said (C_{1-6}) alkyl and (C_{3-7}) cycloalkyl being optionally substituted with R^{160} ;
- g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, and heterocycle being optionally substituted with R^{160} ;
- h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160} ; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160} ;
- i) COR^{127} wherein R^{127} is H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160} ;
- j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, said (C_{1-6}) alkyl and (C_{3-7}) cycloalkyl being optionally substituted with R^{160} ; and

k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160} ;

wherein R^{160} is defined as 1 or 2 substituents selected from: halogen, CN, C_{1-6} alkyl, haloalkyl, COOR^{161} , OR^{161} , $\text{N}(\text{R}^{162})_2$, $\text{SO}_2\text{N}(\text{R}^{162})_2$, $\text{NR}^{162}\text{COR}^{162}$ or $\text{CON}(\text{R}^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

15. The compound according to claim 14, wherein R^2 is selected from: aryl or Het, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, N_3 , or

- a) (C_{1-6}) alkyl optionally substituted with OH, $\text{O}(\text{C}_{1-6})$ alkyl or $\text{SO}_2(\text{C}_{1-6})$ alkyl);
- b) (C_{1-6}) alkoxy;
- e) $\text{NR}^{111}\text{R}^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or R^{112} is 6- or 10-membered aryl, Het, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-Het; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, Het, alkyl-aryl or alkyl-Het; being optionally substituted with halogen or:

- OR^{2h} or $\text{N}(\text{R}^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6}) alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle;

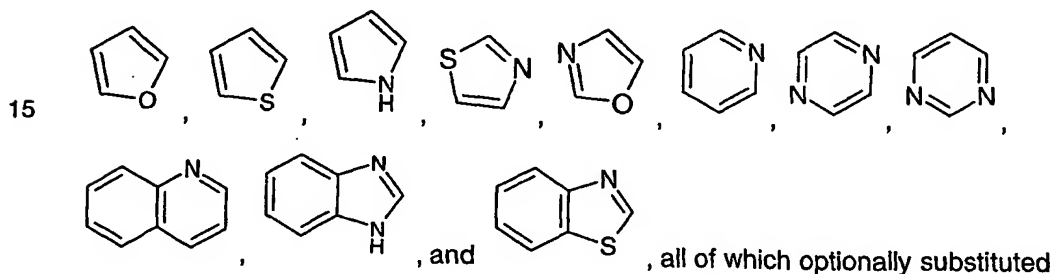
- f) NHCOR^{117} wherein R^{117} is (C_{1-6}) alkyl, $\text{O}(\text{C}_{1-6})$ alkyl or $\text{O}(\text{C}_{3-7})$ cycloalkyl;
- l) CO-aryl; and
- k) CONH_2 , $\text{CONH}(\text{C}_{1-6})$ alkyl, $\text{CON}(\text{C}_{1-6})$ alkyl $_2$, CONH-aryl, or CONHC_{1-6} alkyl aryl.

16. The compound according to claim 15, wherein R^2 is aryl or Het, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, or

- a) (C_{1-6}) alkyl optionally substituted with OH, $O(C_{1-6})$ alkyl or $SO_2(C_{1-6})$ alkyl);
- b) (C_{1-6}) alkoxy; and
- e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or R^{112} is 6- or 10-membered aryl, Het, (C_{1-6}) alkyl-aryl or (C_{1-6}) alkyl-Het; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, Het, alkyl-aryl or alkyl-Het; or being optionally substituted with halogen or:

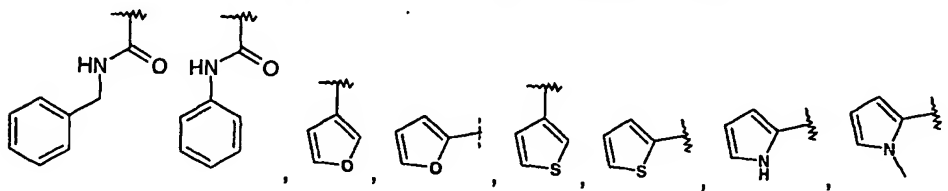
- OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6}) alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle.

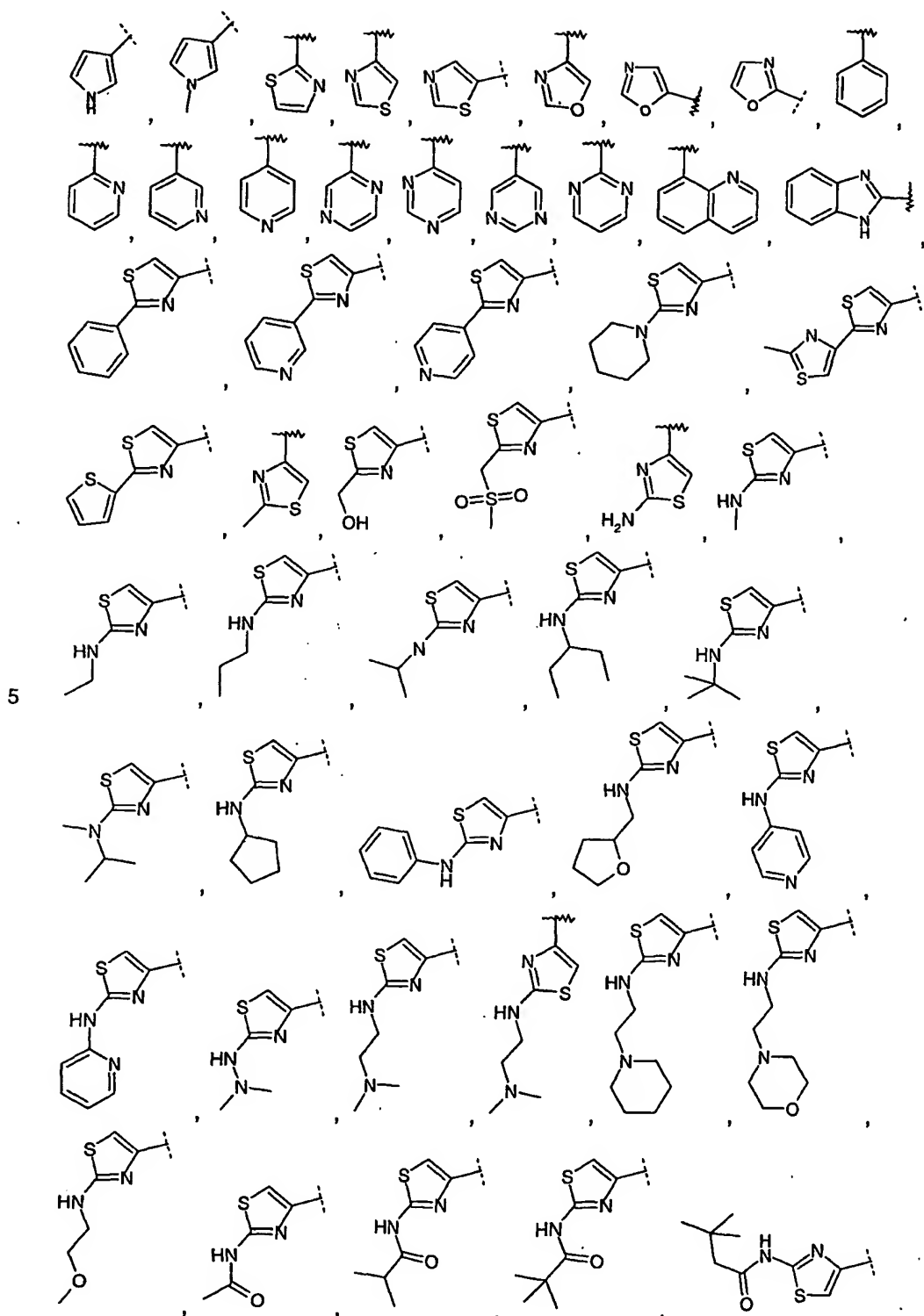
17. The compound according to claim 16, wherein R^2 is phenyl or a heterocycle selected from:

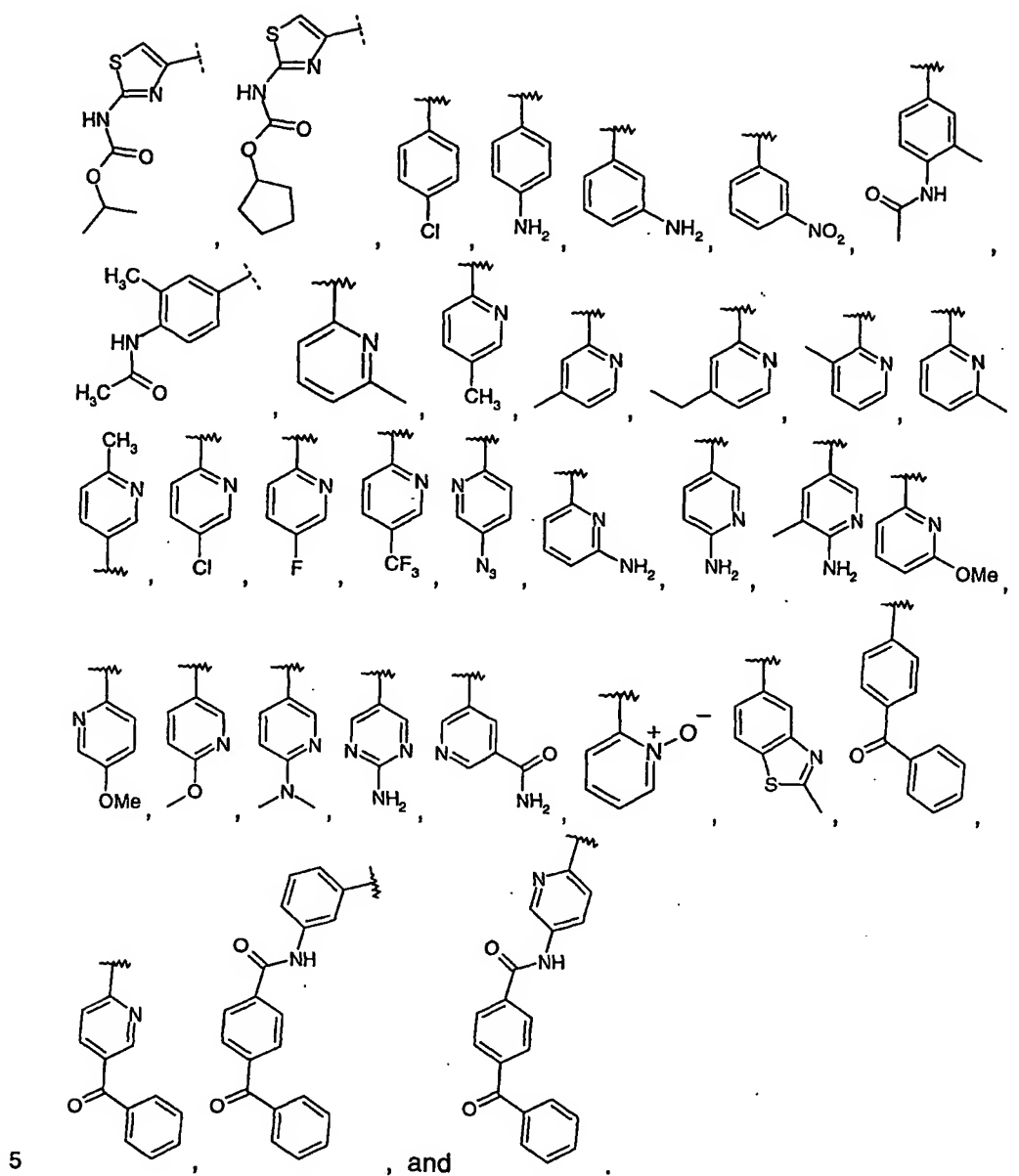


as defined in claim 16.

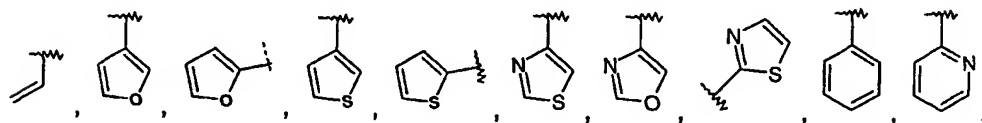
18. The compound according to claim 17, wherein R^2 is selected from the group consisting of: H, Br, $CONHCH_3$, $CON(CH_3)_2$, $CONH_2$, $CH=CH_2$,

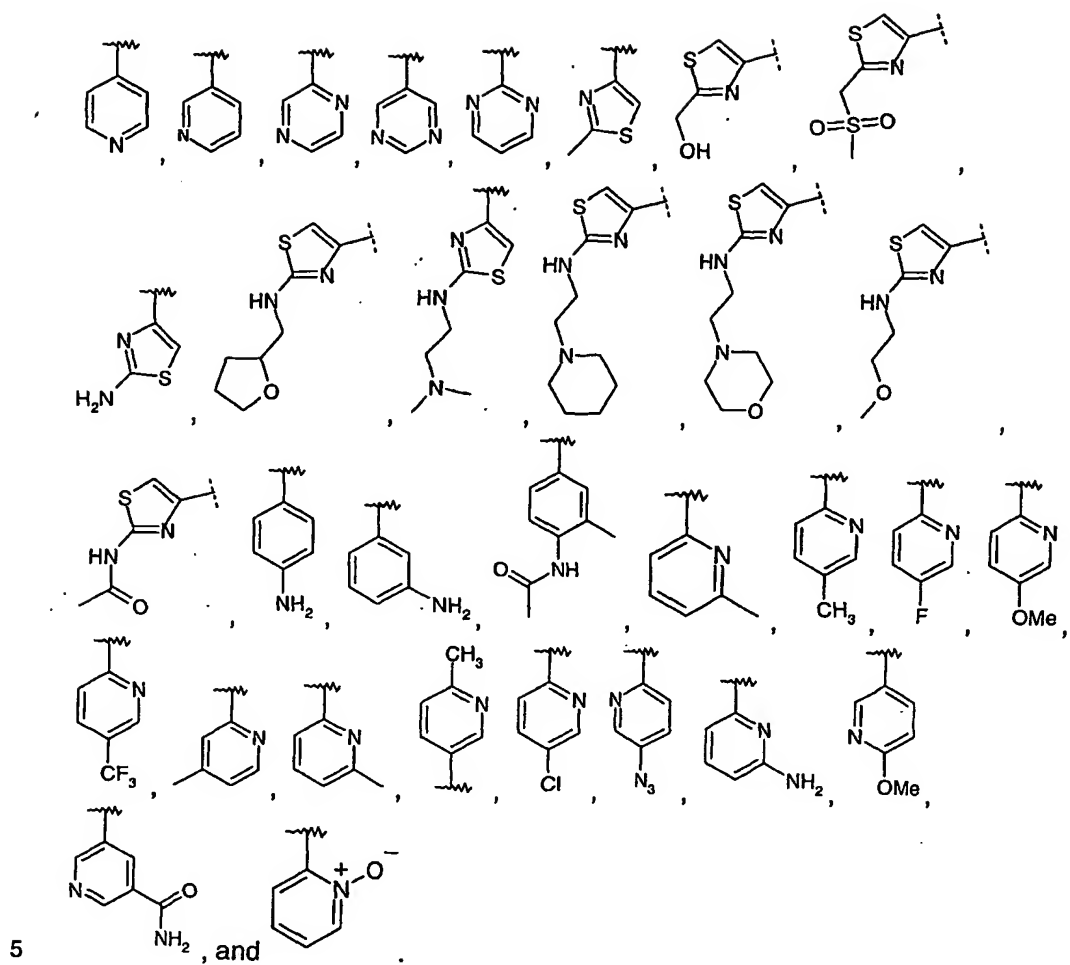




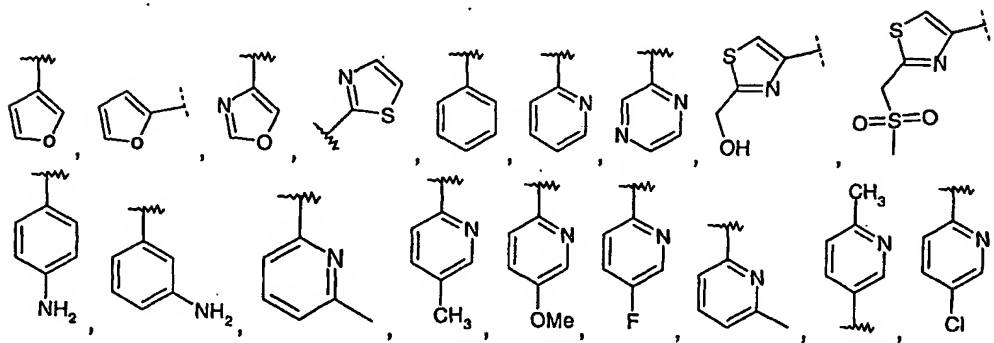


19. The compound according to claim 18, wherein R^2 is selected from:

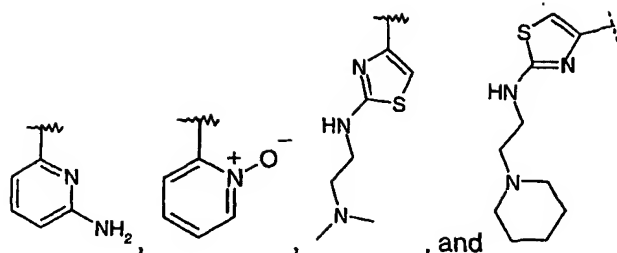




20. The compound according to claim 19, wherein R^2 is selected from:



234



21. The compound according to claim 1, wherein R^3 is selected from (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkenyl, (C_{6-10}) bicycloalkyl, (C_{6-10}) bicycloalkenyl, 6- or 10-membered aryl, or **Het**.

22. The compound according to claim 21, wherein R^3 is (C_{3-7}) cycloalkyl.

23. The compound according to claim 22, wherein R^3 is cyclopentyl, or cyclohexyl.

5

24. The compound according to claim 1, wherein Y^1 is O.

25. The compound according to claim 1, wherein Z is OR^6 wherein R^6 is (C_{1-6}) alkyl substituted with 1 to 4 substituents selected from:

- a) (C_{1-6}) alkyl substituted with R^{150a} , haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150} , wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b} , SR^{150b} , SO_2R^{150b} , $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6} alkyl;
- b) OR^{104} wherein R^{104} is (C_{1-6}) alkyl substituted with R^{150} , (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;
- c) SR^{108a} , $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-

20

- membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with **R**¹⁵⁰, wherein **R**^{108a} is the same as **R**¹⁰⁸ but is not H or unsubstituted C₁₋₆alkyl;
- e) **NR**¹¹¹**R**¹¹² wherein **R**¹¹¹ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and **R**¹¹² is H, CN, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, provided that when **R**¹¹¹ is H or unsubstituted alkyl, **R**¹¹² is not H or unsubstituted alkyl, or **R**¹¹² is also **COOR**¹¹⁵ or **SO₂R**^{115a} wherein **R**¹¹⁵ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and **R**^{115a} is the same as **R**¹¹⁵ but is not H or unsubstituted alkyl, or both **R**¹¹¹ and **R**¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with **R**¹⁵⁰;
- f) **NR**¹¹⁶**COR**¹¹⁷ wherein **R**¹¹⁶ and **R**¹¹⁷ is each (C₁₋₆alkyl) substituted with **R**¹⁵⁰, (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁵⁰;
- g) **NR**¹¹⁸**CONR**¹¹⁹**R**¹²⁰, wherein **R**¹¹⁸, **R**¹¹⁹ and **R**¹²⁰ is each H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or **R**¹¹⁸ is covalently bonded to **R**¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or **R**¹¹⁹ and **R**¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with **R**¹⁵⁰;
- h) **NR**¹²¹**COCOR**¹²² wherein **R**¹²¹ is H or C₁₋₆alkyl and **R**¹²² is **OR**¹²³ or **N(R**¹²⁴**)₂** wherein **R**¹²³ and each **R**¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or **R**¹²⁴ is OH or O(C₁₋₆alkyl) or both **R**¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with **R**¹⁵⁰;
- j) **COOR**¹²⁸ wherein **R**¹²⁸ is (C₁₋₆alkyl) substituted with **R**¹⁵⁰, (C₃₋₇)cycloalkyl,

or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, provided that when R¹²⁹ is H or unsubstituted alkyl, R¹³⁰ is not H or unsubstituted alkyl, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰, wherein R¹⁵⁰ is:

- 1 to 3 substituents selected from: halogen or azido; or

- 1 to 3 substituents selected from:

a) (C₁₋₆)alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;

b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl,

Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;

f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;

g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁶⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁶⁰;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰, and

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to

form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰,

5 wherein, R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and R¹⁶² are as defined above.

26. The compound according to claim 25, wherein Z is OR⁶ wherein R⁶ is (C₁₋₆alkyl)aryl substituted with 1 to 4 substituents selected from:

- 10 a) (C₁₋₆alkyl) substituted with R^{150a}, haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R¹⁵⁰, wherein R^{150a} is the same as R¹⁵⁰ but is not COOR^{150b}, N(R^{150b})₂, NR^{150b}C(O)R^{150b}, OR^{150b}, SR^{150b}, SO₂R^{150b}, SO₂N(R^{150b})₂, wherein R^{150b} is H or unsubstituted C₁₋₆alkyl;
- 15 b) OR¹⁰⁴ wherein R¹⁰⁴ is (C₁₋₆alkyl) substituted with R¹⁵⁰, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 20 d) SO₃H, SO₂N(R^{108a})₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl and aryl, said alkyl and aryl being optionally substituted with R¹⁵⁰, wherein R^{108a} is the same as R¹⁰⁸ but is not H or unsubstituted C₁₋₆alkyl;
- 25 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, (C₁₋₆)alkyl, provided that when R¹¹¹ is H or unsubstituted alkyl, R¹¹² is not H or unsubstituted alkyl, or R¹¹² is also COOR¹¹⁵ or SO₂R^{115a} wherein R¹¹⁵ is H, (C₁₋₆)alkyl or (C₁₋₆alkyl)aryl, and R^{115a} is C₁₋₆alkyl substituted with R¹⁵⁰ or (C₁₋₆alkyl)aryl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the
- 30 nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;

- f) $\text{NR}^{116}\text{COR}^{117}$ wherein R^{116} and R^{117} is each (C_{1-6}) alkyl substituted with R^{150} , (C_{3-7}) cycloalkyl, aryl, Het, said (C_{3-7}) cycloalkyl, aryl, Het being optionally substituted with R^{150} ;
- g) $\text{NR}^{118}\text{CONR}^{119}\text{R}^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, aryl, Het, said alkyl, aryl and Het being optionally substituted with R^{150} ;
- h) $\text{NR}^{121}\text{COCOR}^{122}$ wherein R^{121} is H or C_{1-6} alkyl and R^{122} is OR^{123} or $\text{N}(\text{R}^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}) alkyl, aryl or Het, or R^{124} is OH or $\text{O}(\text{C}_{1-6})$ alkyl, said alkyl, aryl and Het being optionally substituted with R^{150} ;
- i) COOR^{128} wherein R^{128} is (C_{1-6}) alkyl substituted with R^{150} ;
- k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, aryl or Het, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, said alkyl, aryl and Het being optionally substituted with R^{150} ;
- l) aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, all of which being optionally substituted with R^{150} , wherein R^{150} is:
- 1 to 3 substituents selected from: halogen or azido; or
 - 1 to 3 substituents selected from:
- a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6}) alkenyl, all of which optionally substituted with R^{160} ;
- b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;
- d) SR^{108} , $\text{SO}_2\text{N}(\text{R}^{108})_2$ or $\text{SO}_2\text{N}(\text{R}^{108})\text{C}(\text{O})\text{R}^{108}$ wherein each R^{108} is independently H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;
- e) $\text{NR}^{111}\text{R}^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, aryl or Het, and R^{112} is H, (C_{1-6}) alkyl, COOR^{115} or $\text{SO}_2\text{R}^{115}$ wherein R^{115} is (C_{1-6}) alkyl, said alkyl, cycloalkyl, aryl or Het being optionally substituted with R^{160} ;
- f) $\text{NR}^{116}\text{COR}^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;
- g) $\text{NR}^{118}\text{CONR}^{119}\text{R}^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;
- h) $\text{NR}^{121}\text{COCOR}^{122}$ wherein R^{121} is H, (C_{1-6}) alkyl and R^{122} is OR^{123} or

$N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}alkyl)$, aryl or Het, or R^{124} is OH or $O(C_{1-6}alkyl)$, said alkyl, aryl and Het being optionally substituted with R^{160} ;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl optionally substituted with R¹⁶⁰; and

k) $\text{CONR}^{129}\text{R}^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160} ; and

wherein R^{160} is defined as 1 or 2 substituents selected from:
 10 tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, SO_3H ,
 SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or
 $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

27. The compound according to claim 1, wherein **Z** is **OR⁶** wherein **R⁶** is (C₂₋₆)alkenyl, (C₁₋₆)alkyl-Het, wherein said alkenyl or alkyl-Het, is optionally substituted with **R⁶⁰**, wherein **R⁶⁰** is:

- 1 to 4 substituents selected from: halogen; or

15 - 1 to 4 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰;

20 **b) OR¹⁰⁴** wherein **R¹⁰⁴** is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with **R¹⁵⁰**.

d) SR^{108} , $\text{SO}_2\text{N}(\text{R}^{108})_2$ or $\text{SO}_2\text{N}(\text{R}^{108})\text{C}(\text{O})\text{R}^{108}$ wherein each R^{108} is independently H, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-7})\text{cycloalkyl}$ or $(\text{C}_{1-6})\text{alkyl}-(\text{C}_{3-7})\text{cycloalkyl}$, aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(\text{C}_{1-6}\text{alkyl})\text{aryl}$ or $(\text{C}_{1-6}\text{alkyl})\text{Het}$ or heterocycle being optionally substituted with R^{150} .

e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R¹¹² is H; CN, (C₁₋

- ₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;
- h)** NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl optionally substituted with R¹⁵⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;
- i)** COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- j)** COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- k)** CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋

- 7)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;
- 5 l) aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰; wherein R¹⁵⁰ is defined as:
- 1 to 3 substituents selected from: halogen or azido; or
 - 1 to 3 substituents selected from:
- 10 a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;
- b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;
- 15 d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;
- 20 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;
- 25 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹⁶ and R¹¹⁷ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;
- 30

₇cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

5 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R¹¹⁹ and R¹²⁰ are covalently bonded
10 together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ is H or (C₁₋₆)alkyl optionally
15 substituted with R¹⁶⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-
20 cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;
25 and

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently
30 bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from:

5 tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SR¹⁶¹, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both R¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

28. The compound according to claim 27, wherein R⁶⁰ is:
- 1 to 4 substituents selected from: halogen; or
 - 10 - 1 to 4 substituents selected from:
 - a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰;
 - b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said alkyl, cycloalkyl, 15 aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁵⁰;
 - d) SO₃H, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl or aryl, said alkyl and aryl being optionally substituted with R¹⁵⁰;
 - 20 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, and R¹¹² is H, (C₁₋₆)alkyl, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl or (C₁₋₆)alkyl)aryl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, 25 cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or heterocycle being optionally substituted with R¹⁵⁰;
 - f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl or Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl or Het being optionally substituted with R¹⁵⁰;
 - 30 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, aryl or Het, said alkyl, aryl and Het being optionally substituted with R¹⁵⁰;
 - h) NR¹²¹COCOR¹²² wherein R¹²¹ is H or (C₁₋₆)alkyl, and R¹²² is OR¹²³ or

$N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C₁₋₆alkyl), aryl or Het, or R^{124} is OH or O(C₁₋₆alkyl), said alkyl, aryl and Het being optionally substituted with R^{150} ;

j) COOR¹²⁸ wherein R^{128} is H or (C₁₋₆alkyl) optionally substituted with R^{150} ;

5 k) CONR¹²⁹R¹³⁰ wherein R^{129} and R^{130} are independently H, (C₁₋₆alkyl), aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{150} ;

l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R^{150} ; wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen; or

10 - 1 to 3 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₂₋₆)alkenyl, all of which optionally substituted with R^{160} ;

b) OR¹⁰⁴ wherein R^{104} is H, (C₁₋₆alkyl), aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

15 d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R^{108} is independently H, (C₁₋₆alkyl), aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

e) NR¹¹¹R¹¹² wherein R^{111} is H, (C₁₋₆alkyl), aryl or Het, and R^{112} is H, (C₁₋₆alkyl), COOR¹¹⁵ or SO₂R¹¹⁵ wherein R^{115} is (C₁₋₆alkyl) or aryl, said alkyl, aryl and Het being optionally substituted with R^{160} ;

20 f) NR¹¹⁶COR¹¹⁷ wherein R^{116} and R^{117} is each H, (C₁₋₆alkyl), aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆alkyl), aryl or Het, said alkyl, aryl and Het being optionally substituted with R^{160} ;

25 h) NR¹²¹COCOR¹²² wherein R^{121} is H or (C₁₋₆alkyl) optionally substituted with R^{160} , and R^{122} is OR¹²³ or N(R¹²⁴)₂ wherein R^{123} and each R^{124} is independently H, (C₁₋₆alkyl), aryl or Het, or R^{124} is OH or O(C₁₋₆alkyl), said alkyl, aryl and Het being optionally substituted with R^{160} ;

30 i) tetrazole, COOR¹²⁸ wherein R^{128} is H or (C₁₋₆alkyl) optionally substituted with R^{160} ; and

k) CONR¹²⁹R¹³⁰ wherein R^{129} and R^{130} are independently H, (C₁₋₆alkyl), aryl or Het, said alkyl, aryl and Het being optionally substituted

with R^{160} ,

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, SO_3H , SR^{161} , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

29. The compound according to claim 1, wherein Z is $N(R^{6a})R^6$ wherein R^{6a} is H or C_{1-6} alkyl and R^6 is (C_{2-6}) alkenyl, aryl, Het, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-Het, wherein said alkenyl, aryl, Het, alkyl-aryl or alkyl-Het, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, OPO_3H , NO_2 , cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$ alkyl or $C(=NH)NHCO(C_{1-6})$ alkyl; or

- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-8}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} ;

b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het being optionally substituted with R^{150} ;

d) SR^{108} , $SO_2NH(C_{1-6})$ alkyl or $SO_2NHC(O)C_{1-6}$ alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)Het, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, or heterocycle being optionally substituted with R^{150} ;

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl,

(C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

5 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

10 said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

15 or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated

20 heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

25 **j)** COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁵⁰;

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l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R¹⁶⁰; wherein, R¹⁶⁰ is selected from:

- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 3 substituents selected from:

- 5 **a)** (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;
- 10 **b)** OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;
- 15 **d)** SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁶⁰;
- 20 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;
- 25 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆)alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁶⁰;
- 30 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋

₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

h) NR¹²¹COCOR¹²² wherein R¹²¹ is H or (C₁₋₆)alkyl optionally substituted with R¹⁶⁰; and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰; and

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both R¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

30. The compound according to claim 29, wherein R^{6a} is H.

31. The compound according to claim 29, wherein R^6 is (C_{2-6}) alkenyl, aryl, Het, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-Het, wherein said alkenyl, aryl, Het, alkyl-aryl, or alkyl-Het, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, NO_2 , cyano, azido; or

- 1 to 4 substituents selected from:

- 5 **a)** (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} ;
- b)** OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het being optionally substituted with R^{150} ;
- 10 **d)** SH, $S(C_{1-6})$ alkyl, SO_3H , $SO_2NH(C_{1-6})$ alkyl or $SO_2NHC(O)C_{1-6}$ alkyl;
- e)** $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)Het, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6}) alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)Het, or heterocycle being optionally substituted with R^{150} ;
- 15 **f)** $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, said (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl being optionally substituted with R^{150} ;
- 20 **g)** $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{150} ;
- 25 **h)** $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, said alkyl, cycloalkyl being optionally substituted with R^{150} ;
- or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}) alkyl or (C_{3-7}) cycloalkyl, or R^{124} is OH or $O(C_{1-6})$ alkyl or both R^{124} are
- 30

covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{150} ;

5 **j)** $COOR^{128}$ wherein R^{128} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl and (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;

10 **k)** $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl, and (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ;

l) aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, all of which being optionally substituted with R^{150} ; and

wherein R^{150} is selected from:

15 - 1 to 3 substituents selected from: halogen, NO_2 , cyano or azido;

- 1 to 3 substituents selected from:

20 **a)** (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{160} ;

b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{160} ;

25 **d)** SH, $S(C_{1-6})$ alkyl, SO_3H , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** or heterocycle being optionally substituted with R^{160} ;

30 **e)** $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, and R^{112} is H, CN, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, aryl, **Het**, (C_{1-6}) alkyl)aryl, (C_{1-6}) alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein

- R¹¹⁵** is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both **R¹¹¹** and **R¹¹²** are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with **R¹⁶⁰**;
- f) NR¹¹⁶COR¹¹⁷** wherein **R¹¹⁶** and **R¹¹⁷** is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with **R¹⁶⁰**;
- g) NR¹¹⁸CONR¹¹⁹R¹²⁰**, wherein **R¹¹⁸**, **R¹¹⁹** and **R¹²⁰** is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or **R¹¹⁹** and **R¹²⁰** are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with **R¹⁶⁰**;
- h) NR¹²¹COCOR¹²²** wherein **R¹²¹** is H, (C₁₋₆)alkyl optionally substituted with **R¹⁶⁰**; and **R¹²²** is **OR¹²³** or **N(R¹²⁴)₂** wherein **R¹²³** and each **R¹²⁴** is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or **R¹²⁴** is OH or O(C₁₋₆)alkyl or both **R¹²⁴** are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** and heterocycle being optionally substituted with **R¹⁶⁰**;
- j) tetrazole, COOR¹²⁸** wherein **R¹²⁸** is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl and (C₁₋₆)alkyl)**Het** being optionally substituted with **R¹⁶⁰**; and
- k) CONR¹²⁹R¹³⁰** wherein **R¹²⁹** and **R¹³⁰** are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both **R¹²⁹** and **R¹³⁰** are covalently

bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

5 wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H or (C₁₋₆)alkyl.

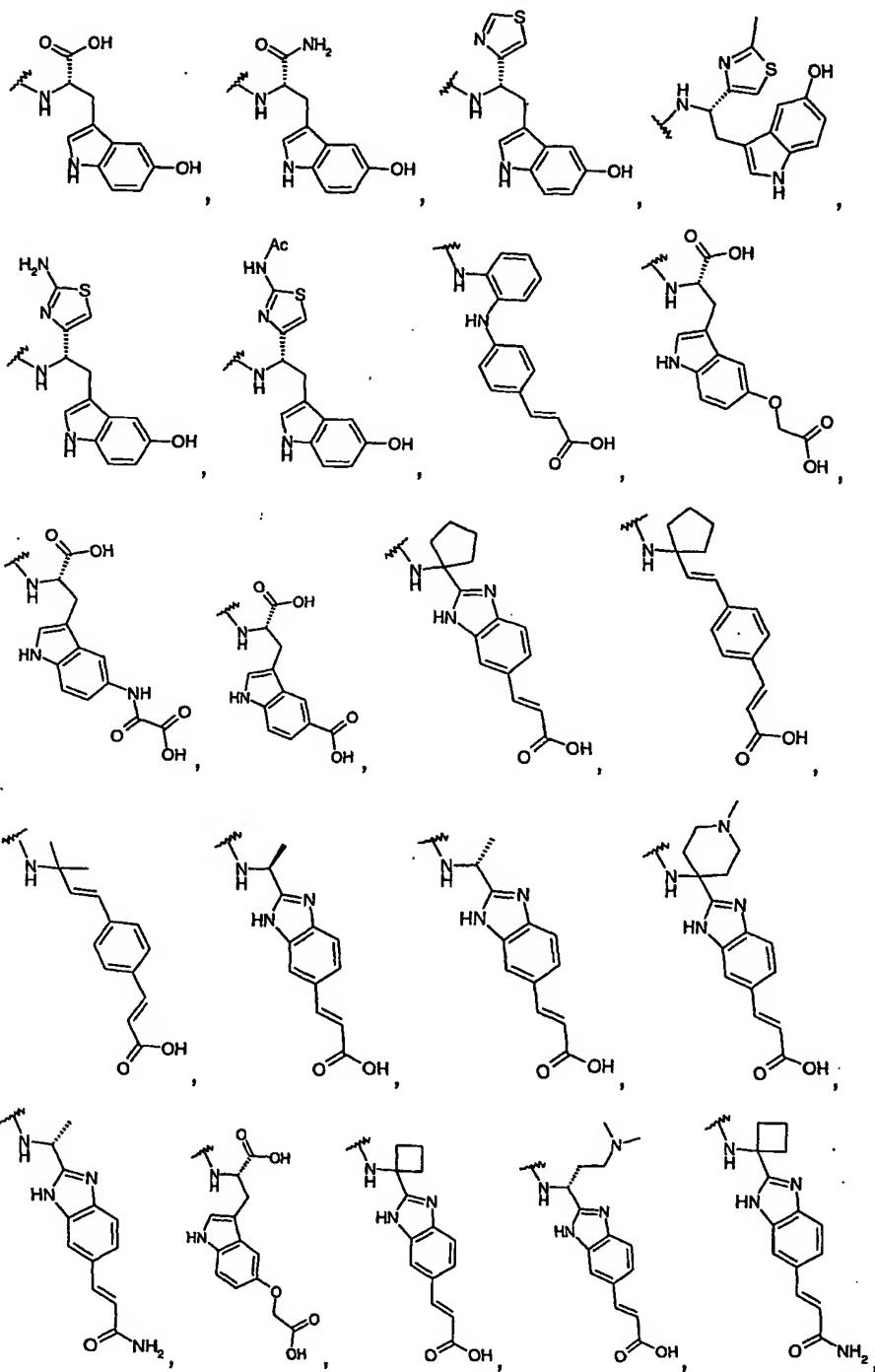
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32. The compound according to claim 31, wherein R⁶ is C₂₋₆alkenyl, phenyl, (C₁₋₆)alkyl-aryl, (C₁₋₆)alkyl-**Het**, wherein said alkenyl, phenyl and the alkyl portion of said alkyl-aryl or alkyl-**Het**, are optionally substituted with 1 to 3 substituents selected from:

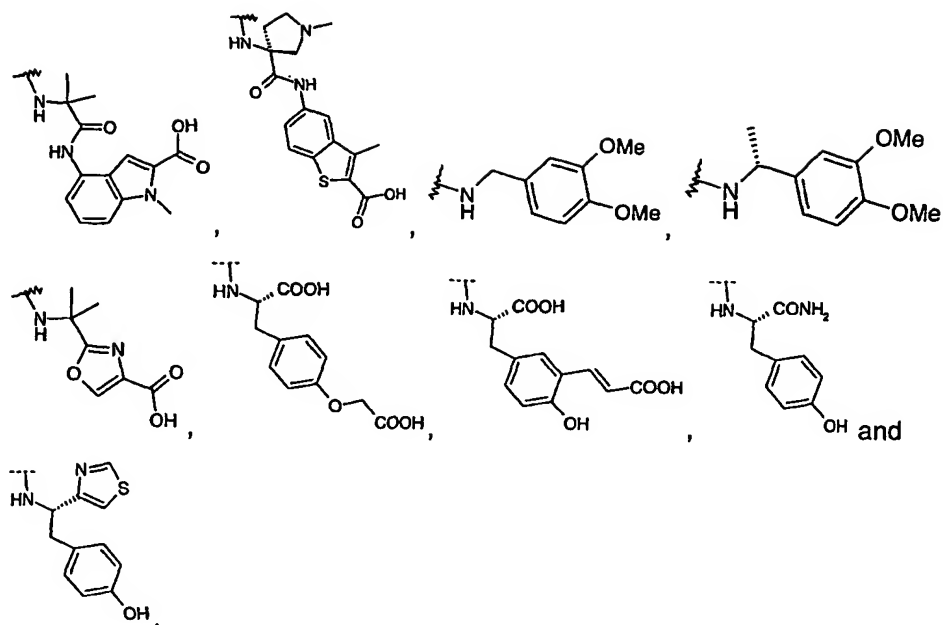
- a) (C₁₋₆) alkyl C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, all of which optionally substituted with C₁₋₆alkyl or C₁₋₆alkoxy, NH₂, NH(Me) or N(Me)₂;
- e) NHR¹¹² wherein R¹¹² is aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, said aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, being optionally substituted with R¹⁵⁰;
- 15 j) COOH;
- k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, and (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 20 l) phenyl or **Het**, both optionally substituted with R¹⁵⁰ and
 wherein R¹⁵⁰ is selected from:
 - 1 or 2 substituents selected from: halogen, NO₂, cyano or azido;
 - 1 or 2 substituents selected from:
- 25 a) (C₁₋₆) alkyl or (C₂₋₆)alkenyl, both optionally substituted with COOH or CONH₂;
- b) OR¹⁰⁴ wherein R¹⁰⁴ is H or (C₁₋₆alkyl) optionally substituted with COOH;
- h) NHCOCOOH;
- 30 j) COOH; and

k) CONH₂

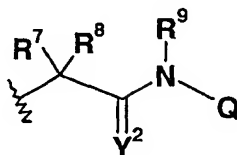
33. The compound according to claim 32, wherein Z is selected from:



255



34. The compound according to claim 29, wherein R^6 is:



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wherein R^7 and R^8 are each independently H, (C_{1-6}) alkyl, haloalkyl, (C_{3-7}) cycloalkyl, 6- or 10-membered aryl, Het, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-Het, wherein said alkyl, cycloalkyl, aryl, Het, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-Het are optionally substituted with R^{70} ; or

10 R^7 and R^8 are covalently bonded together to form second (C_{3-7}) cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when Z is $N(R^{6a})R^6$, either of R^7 or R^8 is covalently bonded to R^{6a} to form a nitrogen-containing 5- or 6-membered heterocycle;

wherein R^{70} is selected from:

- 15
- 1 to 4 substituents selected from: halogen, NO_2 , cyano, azido; or
 - 1 to 4 substituents selected from:
 - a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7}) cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which optionally substituted with R^{150} ;

- b) OR^{104} wherein R^{104} is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R^{150} ;
- 5 d) SR^{108} , $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R^{150} ;
- 10 e) $NR^{111}R^{112}$ wherein R^{111} is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R^{112} is H, CN, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R^{150} ;
- 15 f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R^{150} ;
- 20 g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118} , R^{119} and R^{120} is each H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R^{150} ;
- 25 h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R^{121} is covalently bonded to R^{122} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R^{150} ;
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- alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;
- i) COR¹²⁷ wherein R¹²⁷ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;
- l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R¹⁵⁰, wherein, R¹⁵⁰ is selected from:
- 1 to 3 substituents selected from: halogen, NO₂, cyano, azido; or
 - 1 to 3 substituents selected from:
 - a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl, optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, all of which optionally substituted with R¹⁶⁰;
 - b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R¹⁶⁰;
 - d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ wherein R¹⁰⁸ is H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R¹⁶⁰;
 - e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, and R¹¹² is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het,

- (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆alkyl)-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;
- 5 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, said (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl being optionally substituted with R¹⁶⁰;
- 10 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R¹⁶⁰;
- 15 h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R¹⁶⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁶⁰;
- 20 i) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, said (C₁₋₆alkyl) and (C₃₋₇)cycloalkyl being optionally substituted with R¹⁶⁰; and
- 25 k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆alkyl) or (C₃₋₇)cycloalkyl, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁶⁰;
- 30 wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂ or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H or (C₁₋₆alkyl).

35. The compound according to claim 34, wherein R^7 and R^8 are each independently H, (C_{1-6}) alkyl, haloalkyl, (C_{3-7}) cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, all of which optionally substituted with from 1 to 4 substituents selected from halogen or:

a) (C_{1-6}) alkyl; and

b) $N(R^{8a'})_2$, COR^{8a} , or $SO_2R^{8a''}$ $COOR^{8a}$, $COCOOR^{8a}$, $CON(R^{8a'})_2$, $COCON(R^{8a'})_2$, wherein each R^{8a} or $R^{8a'}$ are independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or each $R^{8a'}$ are independently covalently bonded together and to the nitrogen to which they are both bonded to form a 5, 6 or 7-membered saturated heterocycle; or $R^{8a''}$ is independently (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl.

or R^7 and R^8 are covalently bonded together to form (C_{3-7}) cycloalkyl, 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S.

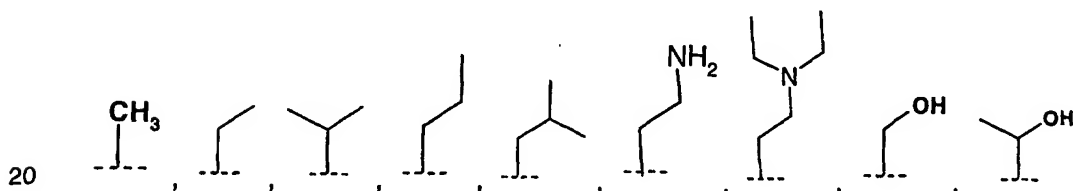
36. The compound according to claim 35, wherein R^7 and R^8 are each independently H, (C_{1-6}) alkyl, haloalkyl, (C_{3-7}) cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**; or R^7 and R^8 are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide;

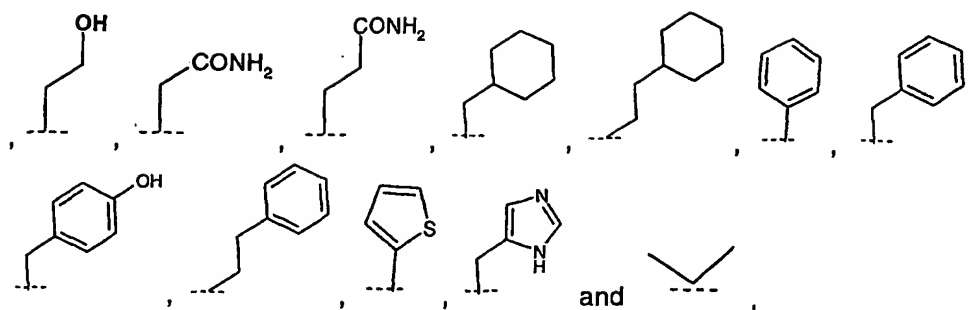
wherein said alkyl, haloalkyl, (C_{3-7}) cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide are optionally monosubstituted with substituents selected from:

a) (C_{1-6}) alkyl; and

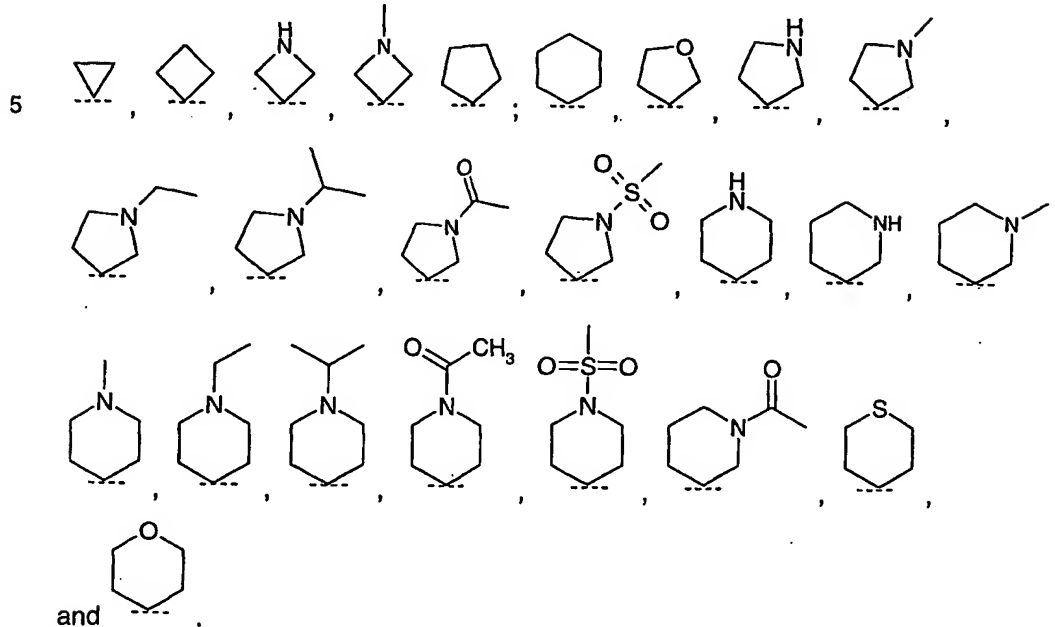
b) NH_2 , $N(CH_2CH)_2$, $COCH_3$, or SO_2CH_3 .

37. The compound according to claim 36, wherein R^7 and R^8 are selected from:

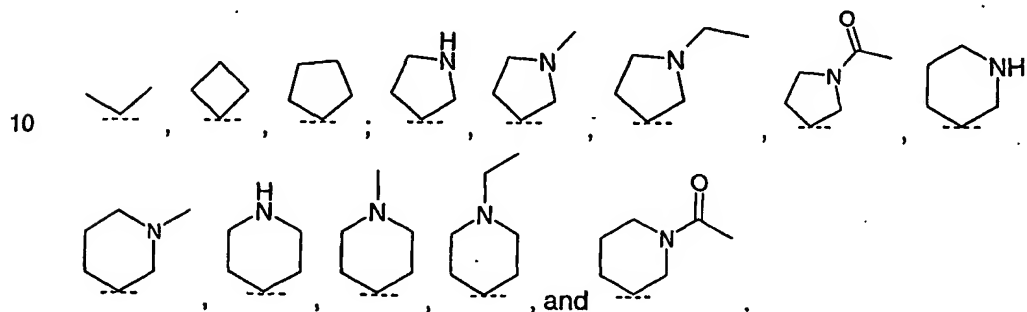




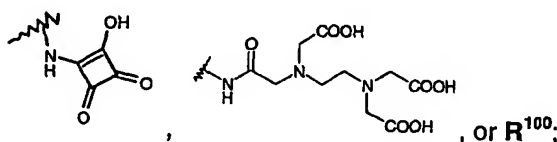
or R^7 and R^8 together form:



38. The compound according to claim 37, wherein **R**⁷ and **R**⁸ are selected from:



39. The compound according to claim 34, wherein R^9 is H, or R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle.
40. The compound according to claim 39, wherein R^9 is H.
41. The compound according to claim 34, wherein Q is a 6- or 10-membered aryl, **Het**, $(C_{1-6}alkyl)aryl$ or $(C_{1-6}alkyl)-Het$, all of which being optionally substituted with:



wherein R^{100} is:

- 5 - 1 to 4 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 4 substituents selected from:
- a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰;
- 10 b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁵⁰;
- 15 d) SR¹⁰⁸ wherein R¹⁰⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, all of which being optionally substituted with R¹⁵⁰;
- e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;
- 20 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, said (C₁₋
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₆alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;

- g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het or heterocycle being optionally substituted with R¹⁵⁰;
- h) NR¹²¹COCOR¹²² wherein R¹²¹ and R¹²² is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, a 6- or 10-membered aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰; or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or R¹²⁴ is OH or O(C₁₋₆alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;
- j) COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)Het being optionally substituted with R¹⁵⁰;
- k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)Het and heterocycle being optionally substituted with R¹⁵⁰;
- l) aryl, Het, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)Het, all of which being optionally substituted with R¹⁵⁰; wherein R¹⁵⁰ is selected from:

- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 3 substituents selected from:

- a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, C₃₋₇ spirocycloalkyl optionally containing 1 or 2 heteroatom, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁶⁰;
- 5 b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁶⁰;
- 10 d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het or heterocycle being optionally substituted with R¹⁶⁰;
- 15 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)Het or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or heterocycle being optionally substituted with R¹⁶⁰;
- 20 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het being optionally substituted with R¹⁶⁰;
- 25 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)Het, or R¹¹⁸ is covalently bonded to R¹¹⁹ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R¹¹⁹ and R¹²⁰ are covalently bonded
- 30

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** or heterocycle being optionally substituted with R¹⁶⁰;

5 h) NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl optionally substituted with R¹⁶⁰, and R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or R¹²⁴ is OH or O(C₁₋₆)alkyl) or both R¹²⁴ are covalently bonded together to form a 5, 10 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

j) tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, 15 said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl and (C₁₋₆)alkyl)**Het** being optionally substituted with R¹⁶⁰; and

k) CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆)alkyl)**Het**, or both R¹²⁹ and R¹³⁰ are covalently 20 bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl, (C₁₋₆)alkyl)**Het** and heterocycle being optionally substituted with R¹⁶⁰;

25 wherein R¹⁶⁰ is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C₁₋₆alkyl, haloalkyl, COOR¹⁶¹, SO₃H, SR¹⁶¹, SO₂R¹⁶¹, OR¹⁶¹, N(R¹⁶²)₂, SO₂N(R¹⁶²)₂, NR¹⁶²COR¹⁶² or CON(R¹⁶²)₂, wherein R¹⁶¹ and each R¹⁶² is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl; or both 30 R¹⁶² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

42. The compound according to claim 41, wherein Q is a 6- or 10-membered

aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)-**Het**, all of which being optionally substituted with:

- 1 to 4 substituents selected from: halogen, NO₂, cyano or azido; or

- 1 to 4 substituents selected from:

a) (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₈)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with R¹⁵⁰;

5 b) OR¹⁰⁴ wherein R¹⁰⁴ is H, (C₁₋₆alkyl), (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

10 d) SR¹⁰⁸, SO₂N(R¹⁰⁸)₂ or SO₂N(R¹⁰⁸)C(O)R¹⁰⁸ wherein each R¹⁰⁸ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with R¹⁵⁰;

15 e) NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, and R¹¹² is H, CN, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het**, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁵⁰;

20 f) NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁵⁰;

25 g) NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated

heterocycle; said alkyl, cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** or heterocycle being optionally substituted with **R**¹⁵⁰;

5 **h)** **NR**¹²¹**COCOR**¹²² wherein **R**¹²¹ is H, (C₁₋₆)alkyl optionally substituted with **R**¹⁵⁰, and **R**¹²² is **OR**¹²³ or **N(R**¹²⁴**)**₂ wherein **R**¹²³ and each **R**¹²⁴ is independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or **R**¹²⁴ is OH or O(C₁₋₆alkyl) or both **R**¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with **R**¹⁵⁰;

10 **j)** **COOR**¹²⁸ wherein **R**¹²⁸ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl and (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁵⁰;

15 **k)** **CONR**¹²⁹**R**¹³⁰ wherein **R**¹²⁹ and **R**¹³⁰ are independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, or both **R**¹²⁹ and **R**¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl, (C₁₋₆alkyl)**Het** and heterocycle being optionally substituted with **R**¹⁵⁰;

20 **l)** aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, all of which being optionally substituted with **R**¹⁵⁰; wherein **R**¹⁵⁰ is selected from:

- 1 to 3 substituents selected from: halogen, NO₂, cyano or azido; or
- 1 to 3 substituents selected from:

25 **a)** (C₁₋₆) alkyl or haloalkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆) alkyl-(C₃₋₇)cycloalkyl, all of which optionally substituted with **R**¹⁶⁰;

b) **OR**¹⁰⁴ wherein **R**¹⁰⁴ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, said alkyl, cycloalkyl, aryl and **Het** being optionally substituted with **R**¹⁶⁰;

30 **c)** **OCOR**¹⁰⁵ wherein **R**¹⁰⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with **R**¹⁶⁰;

d) **SR**¹⁰⁸, **SO₂N(R**¹⁰⁸**)**₂ or **SO₂N(R**¹⁰⁸**)C(O)R**¹⁰⁸ wherein each **R**¹⁰⁸ is

independently H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or both R¹⁰⁸ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl or heterocycle being optionally substituted with R¹⁶⁰;

5 **e)** NR¹¹¹R¹¹² wherein R¹¹¹ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, and R¹¹² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, COOR¹¹⁵ or SO₂R¹¹⁵ wherein R¹¹⁵ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or both R¹¹¹ and R¹¹² are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C₁₋₆)alkyl)aryl or (C₁₋₆alkyl)**Het**, or heterocycle being optionally substituted with R¹⁶⁰;

10 **f)** NR¹¹⁶COR¹¹⁷ wherein R¹¹⁶ and R¹¹⁷ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het**, said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, **Het**, (C₁₋₆alkyl)aryl or (C₁₋₆alkyl)**Het** being optionally substituted with R¹⁶⁰;

15 **g)** NR¹¹⁸CONR¹¹⁹R¹²⁰, wherein R¹¹⁸, R¹¹⁹ and R¹²⁰ is each H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, or R¹¹⁹ and R¹²⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R¹⁶⁰;

20 **h)** NR¹²¹COCOR¹²² wherein R¹²¹ is H, (C₁₋₆)alkyl optionally substituted with R¹⁶⁰, or R¹²² is OR¹²³ or N(R¹²⁴)₂ wherein R¹²³ and each R¹²⁴ is independently H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, or R¹²⁴ is OH or O(C₁₋₆alkyl), or both R¹²⁴ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R¹⁶⁰;

25 **j)** tetrazole, COOR¹²⁸ wherein R¹²⁸ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, said (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl being optionally substituted with R¹⁶⁰; and

30 **k)** CONR¹²⁹R¹³⁰ wherein R¹²⁹ and R¹³⁰ are independently H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl, or both R¹²⁹ and R¹³⁰ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6

or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160} ;

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6} alkyl, haloalkyl, $COOR^{161}$, SO_3H , SO_2R^{161} , OR^{161} , $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl or (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

43. The compound according to claim 42, wherein **Q** is a 6- or 10-membered aryl or **Het**, both being optionally substituted with:

- 1 to 3 halogen, NO_2 , cyano, azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, first (C_{3-7}) cycloalkyl, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which are optionally substituted with R^{150} ;

b) OR^{104} wherein R^{104} is H, (C_{1-6}) alkyl;

d) SO_2NHR^{108} wherein R^{108} is H or (C_{1-6}) alkyl;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H or (C_{1-6}) alkyl;

f) $NHCOR^{117}$ wherein R^{116} is H or (C_{1-6}) alkyl;

g) $NHCONR^{119}R^{120}$, wherein R^{119} and R^{120} is each independently H or (C_{1-6}) alkyl;

h) $NHCOCOR^{122}$ wherein R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H or (C_{1-6}) alkyl;

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6}) alkyl;

k) $CONHR^{130}$ wherein R^{130} is H, (C_{1-6}) alkyl;

l) 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het**, said aryl, **Het**, (C_{1-6}) alkyl)aryl or (C_{1-6}) alkyl)**Het** being optionally substituted with R^{150} ; wherein R^{150} is selected from:

- 1 to 3 halogens; or

- 1 to 3 substituents selected from:

a) first (C_{1-6}) alkyl or haloalkyl, first (C_{3-7}) cycloalkyl, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) alkyl- (C_{3-7}) cycloalkyl, all of which are optionally

substituted with tetrazole, OR^{102} , COOR^{102} , wherein R^{102} is H or $(\text{C}_{1-6})\text{alkyl}$;

b) OR^{104} wherein R^{104} is H, $(\text{C}_{1-6})\text{alkyl}$;

d) $\text{SO}_2\text{NHR}^{108}$ wherein R^{108} is H or $(\text{C}_{1-6})\text{alkyl}$;

5 e) $\text{NR}^{111}\text{R}^{112}$ wherein both R^{111} and R^{112} are independently H or $(\text{C}_{1-6})\text{alkyl}$;

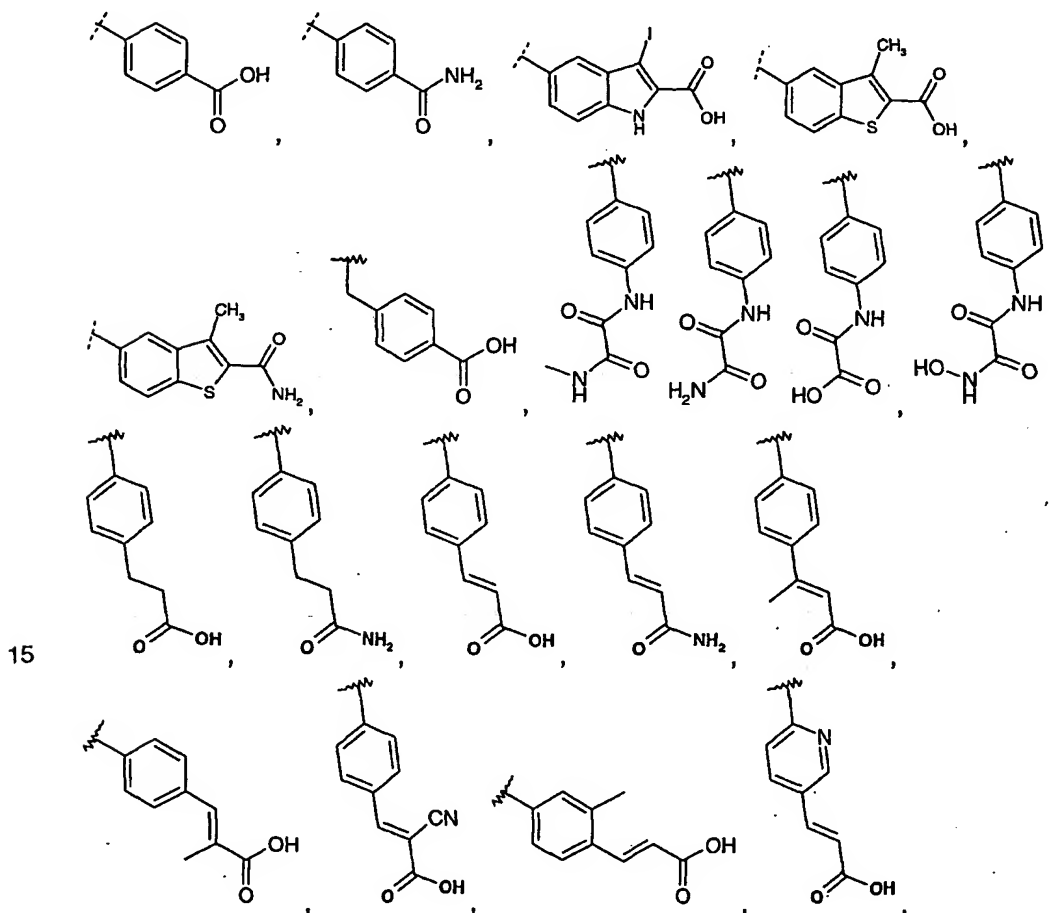
f) NHCOR^{117} wherein R^{116} is H or $(\text{C}_{1-6})\text{alkyl}$; and

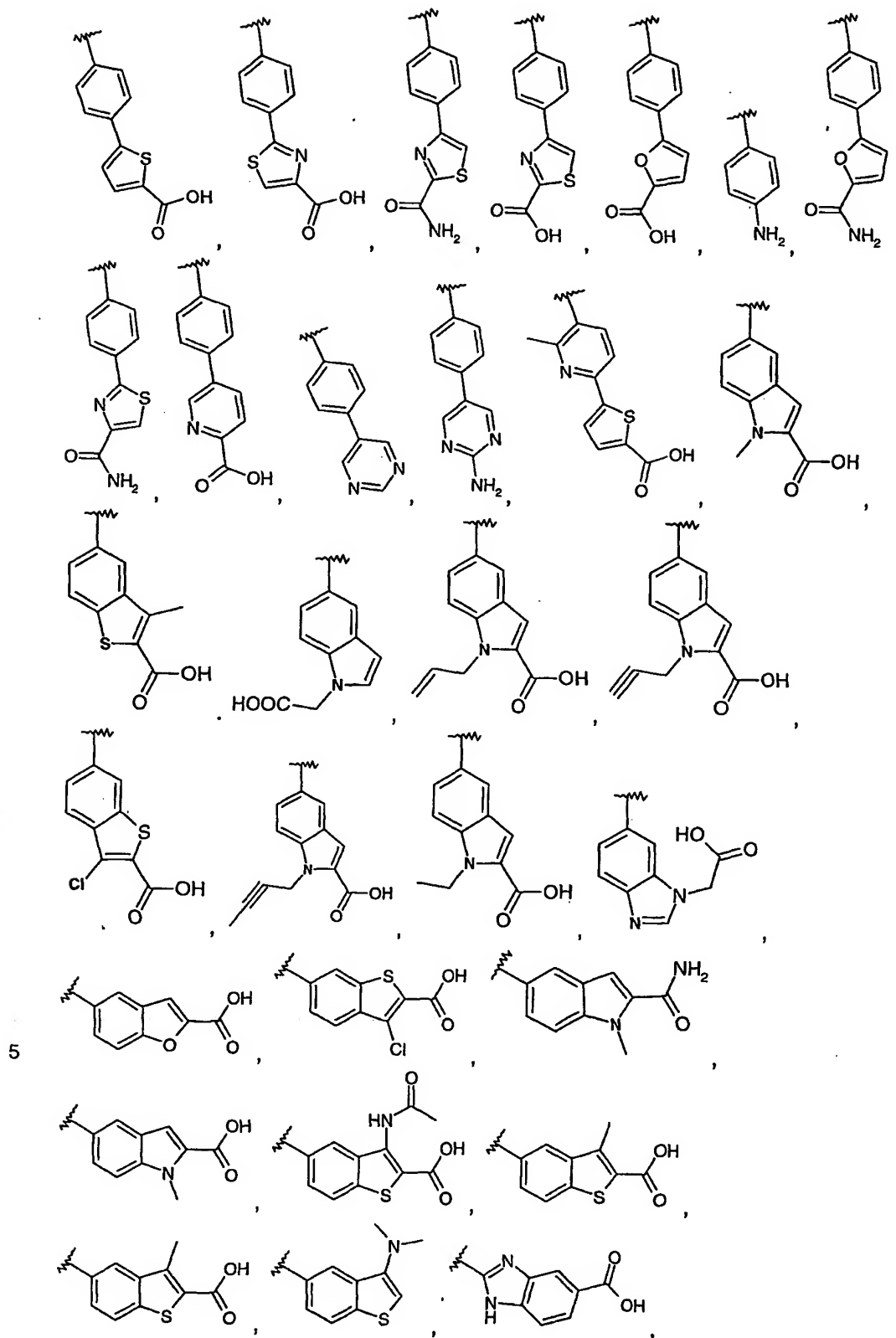
h) NHCOCOR^{122} wherein R^{122} is OR^{123} or $\text{N}(\text{R}^{124})_2$ wherein R^{123} and each R^{124} is independently H or $(\text{C}_{1-6})\text{alkyl}$;

10 j) COOR^{128} wherein R^{128} is H, $(\text{C}_{1-6})\text{alkyl}$; and

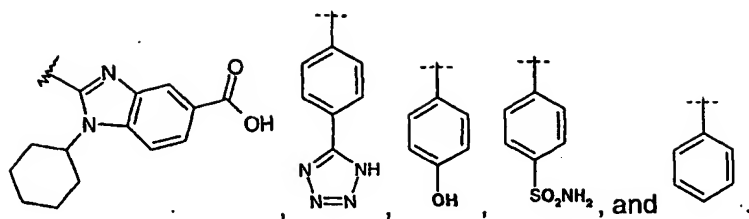
k) CONHR^{130} wherein R^{130} is H, $(\text{C}_{1-6})\text{alkyl}$.

44. The compound according to claim 43, wherein Q is selected from:

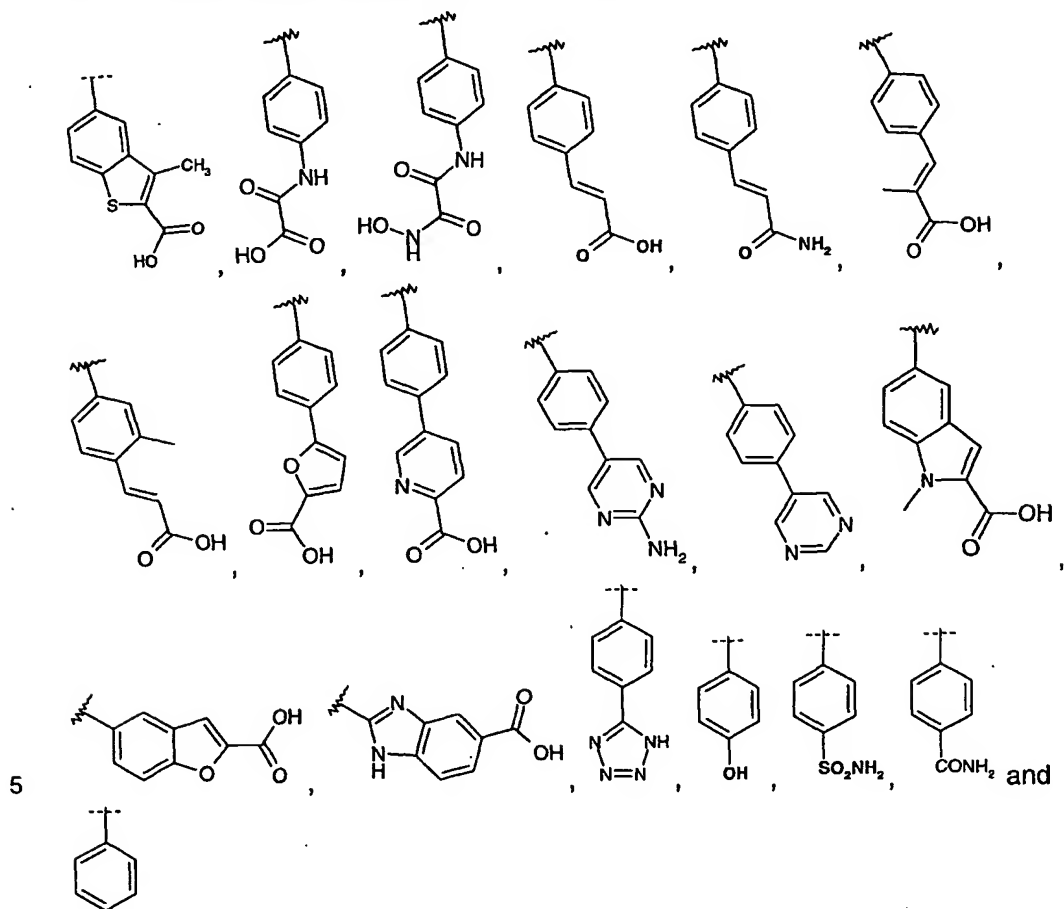




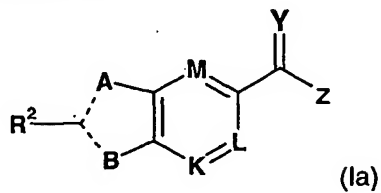
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45. The compound according to claim 44, wherein Q is selected from:



46. A compound represented by Formula Ia:



wherein:

A is O, S, NR¹, or CR¹;

B is NR^3 or CR^3 ;

R¹ is selected from the group consisting of: H, (C₁₋₆)alkyl, benzyl, (C₁₋₆ alkyl)-(C₆₋₁₀aryl), (C₁₋₆ alkyl)-5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, and 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said benzyl and said heteroatom are optionally substituted with from 1 to 4 substituents selected from the group consisting of: COOH, COO(C₁₋₆alkyl), halogen, and (C₁₋₆ alkyl);

10

R² is selected from the group consisting of: H, halogen, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, phenyl, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, pyridine-N-oxide, and 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S,

15

said phenyl, heterocycle and heterobicycle being optionally substituted with from 1 to 4 substituents selected from the group consisting of: halogen, C(halogen)₃, (C₁₋₆)alkyl, OH, O(C₁₋₆ alkyl), NH₂, and N(C₁₋₆ alkyl)₂;

R³ is selected from the group consisting of: 5-, 6- or 7-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, norbornane, (C₃₋₇)cycloalkyl and (C₃₋₇)cycloalkyl-(C₁₋₆ alkyl);

20

M is N, CR^4 , or COR^5 , wherein **R**⁴ is selected from the group consisting of: H, halogen, and (C₁₋₆ alkyl); and **R**⁵ is selected from the group consisting of: H and (C₁₋₆ alkyl);

25

K and **L** is N or CH;

----- represents either a single or a double bond;

30

Y is O or S;

Z is OR^6 or NR^6R^{6a}

R⁶ is selected from the group consisting of: H, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₆)alkyl, (C₆₋₁₀)aryl, (C₆₋₁₀)aryl(C₁₋₆)alkyl, (C₂₋₆)alkenyl,

35

(C₃₋₆)cycloalkyl(C₂₋₆)alkenyl, (C₆₋₁₀)aryl(C₂₋₆)alkenyl, N{(C₁₋₆) alkyl}₂, NHCOO(C₁₋₆)alkyl(C₆₋₁₀)aryl, NHCO(C₆₋₁₀)aryl, (C₁₋₆)alkyl-5- or 6-atom heterocycle, having 1 to 4 heteroatoms selected from O, N and S, and 9- or 10-atom heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

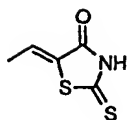
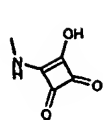
5 wherein said alkyl, cycloalkyl, aryl, alkenyl, heterocycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C₁₋₆)alkyl, (C₁₋₆)alkyl, (C₁₋₆)alkyl-hydroxy, phenyl, benzyloxy, halogen, (C₂₋₄)alkenyl, (C₂₋₄)alkenyl-(C₁₋₆)alkyl-COOH, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

10 wherein said alkyl, cycloalkyl, aryl, alkenyl and heterocycle being optionally substituted with from 1 to 4 substituents selected from: (C₁₋₆ alkyl), CF₃, OH, COOH, NHC(C₁₋₆alkyl)₂, NHCO(C₁₋₆ alkyl), NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

15 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S, said heterobicycle being optionally substituted with from 1 to 4 substituents selected from:

20 halogen, OPO₃H, sulfonamido, SO₃H, SO₂CH₃, -CONH₂, -COCH₃, (C₁₋₃)alkyl, (C₂₋₄alkenyl)COOH, tetrazolyl, COOH, -CONH₂, triazolyl, OH, NO₂, NH₂, -O(C₁₋₆ alkyl)COOH, hydantoin, benzoyleneurea, (C₁₋₄)alkoxy, cyano, azido, -O-(C₁₋₆)alkyl COOH, -O-(C₁₋₆)alkyl COO-(C₁₋₆)alkyl, NHCO(C₁₋₆ alkyl), -NHCOCOOH, -NHCOCONHOH, -NHCOCOCONH₂,
25 -NHCOCONHCH₃, -NHCO(C₁₋₆)alkyl-COOH, -NHCOCONH(C₁₋₆)alkyl-COOH, -NHCO(C₃₋₇)cycloalkyl-COOH, -NHCONH(C₆₋₁₀)aryl-COOH, -NHCONH(C₆₋₁₀)aryl-COO(C₁₋₆)alkyl, -NHCONH(C₁₋₆)alkyl-COOH, -NHCONH(C₁₋₆)alkyl-(C₂₋₆)alkenyl-COOH, -NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-O(C₁₋₆)alkyl COOH, -NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-COOH, -NHCH₂COOH, -NHCONH₂,
30 -NHCO(C₁₋₆)hydroxyalkyl COOH, -OCO(C₁₋₆)hydroxyalkyl COOH, (C₃₋₆)cycloalkyl COOH,

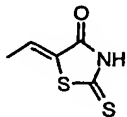
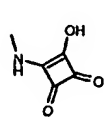
274



, -NHCN, -NHCHO, -NH₂SO₂CH₃, and
-NH₂SO₂CF₃;

6- or 10-membered aryl being optionally substituted with from 1 to 4
substituents selected from:

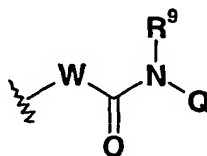
- 5 halogen, OPO₃H, sulfonamido, SO₃H, SO₂CH₃, -CONH₂,
-COCH₃, (C₁₋₃)alkyl, (C₂₋₄alkenyl)COOH, tetrazolyl, COOH,
-CONH₂, triazolyl, OH, NO₂, NH₂, -O(C₁₋₆ alkyl)COOH,
hydantoin, benzoyleneurea, (C₁₋₄)alkoxy, cyano, azido,
-O-(C₁₋₆)alkyl COOH, -O-(C₁₋₆)alkyl COO-(C₁₋₆)alkyl, NHCO(C₁₋₆
10 alkyl), -NHCOCOOH, -NHCOCONHOH, -NHCOCONH₂,
-NHCOCONHCH₃, -NHCO(C₁₋₆)alkyl-COOH,
-NHCOCONH(C₁₋₆)alkyl-COOH, -NHCO(C₃₋₇)cycloalkyl-
COOH, -NHCONH(C₆₋₁₀)aryl-COOH, -NHCONH(C₆₋₁₀)aryl-
COO(C₁₋₆)alkyl, -NHCONH(C₁₋₆)alkyl-COOH, -NHCONH(C₁₋₆
15 alkyl-COO(C₁₋₆)alkyl, -NHCONH(C₁₋₆)alkyl-(C₂₋₆)alkenyl-
COOH, -NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-O(C₁₋₆)alkyl COOH, -NH(C₁₋₆)
alkyl-(C₆₋₁₀)aryl-COOH, -NHCH₂COOH, -NHCONH₂,
-NHCO(C₁₋₆)hydroxyalkyl COOH, -OCO(C₁₋₆)hydroxyalkyl
COOH, (C₃₋₆)cycloalkyl COOH,



, -NHCN, -NHCHO, -NH₂SO₂CH₃, and
-NH₂SO₂CF₃;

coumarin, (C₁₋₆)alkyl-amino, NH(C₁₋₆ alkyl), C(halogen)₃,
-NH(C₂₋₄)acyl, -NH(C₆₋₁₀)aroyl, -O(C₁₋₆alkyl)-Het;

- 25 **R**^{6a} is H or (C₁₋₆ alkyl) covalently bonded to either **R**⁷ or **R**⁸ to form pyrrolidine;
or **Z** is



wherein

- W** is CR^7R^8 wherein R^7 and R^8 are each independently H, (C_{1-6} alkyl), (C_{3-7} cycloalkyl), (C_{1-6} alkyl)phenyl, (C_{1-6} alkyl)-(C_{3-7} cycloalkyl), (C_{3-7} cycloalkyl)-(C_{1-6} alkyl), (C_{3-7} cycloalkyl)-(C_{2-4} alkenyl), (C_{1-6} alkyl)-OH, phenyl, CH_2 biphenyl, 5- or
- 5 6-membered heterocycle having from 1 to 4 heteroatoms selected from O, N, and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, (C_{1-6} alkyl)-5- or 6-membered heterocycle having from 1 to 4 heteroatoms selected from O, N, and S, or (C_{1-6} alkyl)-9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S,
- 10 or R^7 and R^8 are covalently bonded together to form (C_{3-7} cycloalkyl), 4-, 5- or 6-membered heterocycle having from 1 to 4 heteroatoms selected from O, N, and S; or one of R^7 or R^8 is covalently bonded to R^9 to form a pyrrolidine;

wherein said alkyl, cycloalkyl, heterocycle, heterobicycle, phenyl are optionally substituted with from 1 to 4 substituents selected from the group

15 consisting of: OH, COOH, (C_{1-6} alkyl), (C_{2-4} alkenyl), CONH_2 , NH_2 , $\text{NH}(\text{C}_{1-6}$ alkyl), $\text{N}(\text{C}_{1-6}$ alkyl) $_2$, NHCOCOOH , $\text{NHCOCO}(\text{C}_{1-6}$ alkyl) $_2$, $\text{NHCOCO}(\text{C}_{1-6}$ alkyl), SH, $\text{S}(\text{C}_{1-6}$ alkyl), $\text{NHC}(=\text{NH})\text{NH}_2$, halogen, and $\text{COO}(\text{C}_{1-6}$ alkyl);

R^9 is H or (C_{1-6} alkyl); and

20

Q is selected from the group consisting of: (C_{1-3} alkyl)CONHaryl, 6-, 9-, or 10-membered aryl, biphenyl, 5- or 6-atom heterocycle having 1 to 4 heteroatoms selected from O, N and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

25

wherein said aryl, biphenyl, heterocycle and heterobicycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, $\text{COO}(\text{C}_{1-6})$ alkyl, (C_{1-6})alkyl, (C_{1-6})alkylCOOH, (C_{1-6} alkyl)(C_{2-4} alkynyl), (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl- (C_{1-6})alkyl-COOH, 5- or 6-membered second heterocycle having 1 to 4

30 heteroatoms selected from O, N and S, NH-5- or 6- membered second heterocycle having 1 to 4 heteroatoms selected from O, N, and S,

35

wherein said second heterocycle and phenyl being optionally substituted with from 1 to 4 substituents selected from: (C_{1-6} alkyl), CF_3 , OH, (C_{1-6} alkyl) COOH, $\text{O}(\text{C}_{1-6}$ alkyl)COOH, (C_{1-6} alkyl) $\text{COO}(\text{C}_{1-6}$ alkyl), CH_2 phenyl, $\text{COO}(\text{C}_{1-6}$ alkyl), (C_{1-6} alkyl) $\text{O}(\text{C}_{1-6}$ alkyl), COOH,

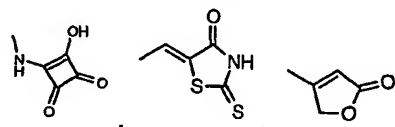
NCH(C₁₋₆alkyl)₂, NCO(C₁₋₆ alkyl), NH₂, NH(C₁₋₆ alkyl), halogen, and N(C₁₋₆ alkyl)₂;

halogen, OPO₃H, benzyl, sulfonamido, SH, SOCH₃, SO₃H, SO₂CH₃, S(C₁₋₆ alkyl)COOH, -CONH₂, -COCH₃, (C₁₋₃)alkyl, (C₂₋₄alkenyl)COOH

5 wherein said alkenyl is optionally substituted with from 1 to 2 (C₁₋₆ alkyl) substituents,

(C₂₋₄alkenyl)COO(C₁₋₆alkyl), tetrazolyl, COOH, triazolyl, OH, NO₂, NH₂, , - O(C₁₋₆ alkyl)COOH, hydantoin, benzoyleneurea, (C₁₋₄)alkoxy, (C₁₋₄)alkoxy(C₁₋₆ alkyl)COOH, cyano, azido, -O-(C₁₋₆)alkyl COOH, -O-(C₁₋₆)alkyl

10 COO-(C₁₋₆)alkyl, -NHCOCOOH, -NHCOCONHOH, -NHCOCONH₂, -NHCOCONHCH₃, -NHCO(C₁₋₆)alkyl-COOH, -NHCOCONH(C₁₋₆)alkyl-COOH, -NHCO(C₃₋₇)cycloalkyl-COOH, -NHCONH(C₆₋₁₀)aryl-COOH, - NHCONH(C₆₋₁₀)aryl-COO(C₁₋₆)alkyl, - NHCONH(C₁₋₆)alkyl-COOH, - NHCONH(C₁₋₆)alkyl-COO(C₁₋₆)alkyl, - NHCONH(C₁₋₆)alkyl-(C₂₋₆)alkenyl-COOH, - NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-O(C₁₋₆)alkyl COOH, - NH(C₁₋₆)alkyl-(C₆₋₁₀)aryl-COOH, -NHCH₂COOH, 15 -NHCONH₂, -NHCO(C₁₋₆)hydroxyalkyl COOH, -OCO(C₁₋₆)hydroxyalkyl COOH, (C₃₋₆)cycloalkyl COOH,

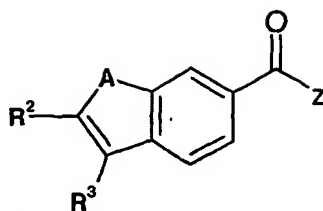


, -NHCN, -NHCHO, -NHSO₂CH₃, -NHSO₂CF₃, coumarin, (C₁₋₆)alkyl-amino, NH(C₁₋₆alkyl)₂, C(halogen)₃, 20 -NH(C₂₋₄)acyl, -NH(C₆₋₁₀)aroyl, -CONH(C₁₋₆alkyl), -CO(C₁₋₆)alkyl-COOH, -CONH(C₁₋₆)alkyl-COOH, -CO-NH-alanyl, -CONH(C₂₋₄)alkylN(C₁₋₆alkyl)₂, -CONH(C₂₋₄) alkyl-Het, -CONH(C₂₋₄) alkyl-(COOH)-Het, -CONH(C₁₋₂ alkyl) (OH)(C₁₋₂ alkyl)OH, -CONH(C₁₋₆) alkyl-COOH, -CONH(C₆₋₁₀ aryl), -CONH-Het, 25 -CONH(C₆₋₁₀) aryl-COOH, -CONH(C₆₋₁₀) aryl-COO(C₁₋₆) alkyl, -CONH(C₁₋₆) alkyl-COO(C₁₋₆) alkyl, -CONH(C₆₋₁₀) aryl-(C₁₋₆)alkyl-COOH, and -CONH(C₆₋₁₀) aryl-(C₂₋₆)alkenyl-COOH,

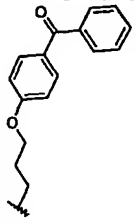
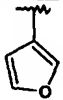
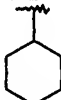
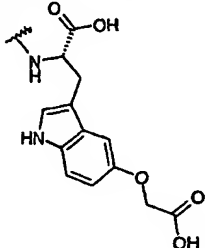
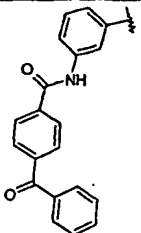
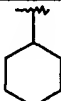
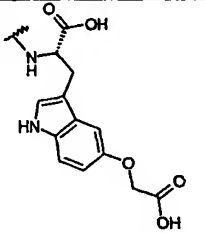
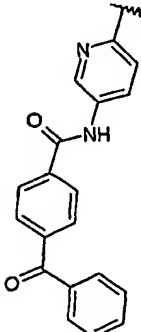
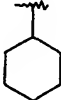
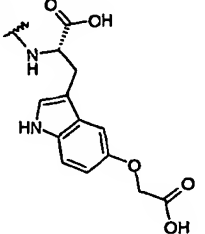
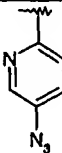
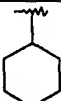
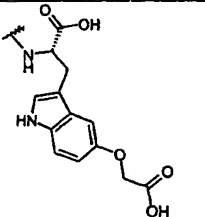
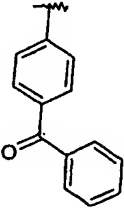
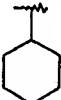
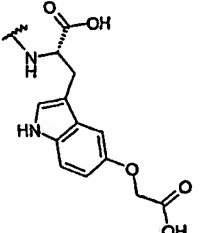
or a salt thereof.

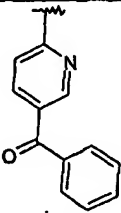
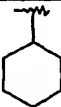
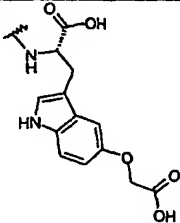
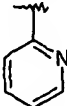

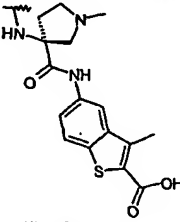
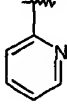
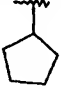
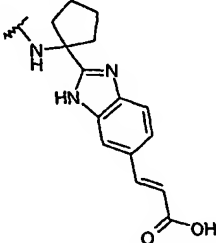
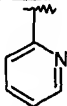
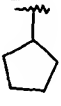
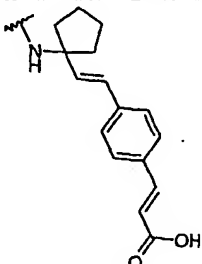
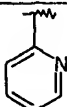
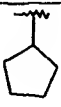
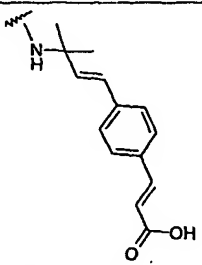
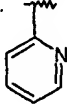
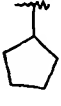
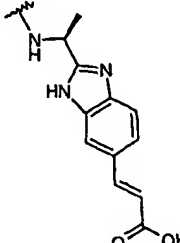
277

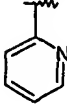
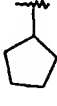
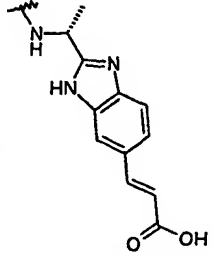
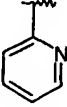
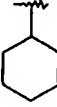
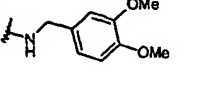
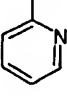

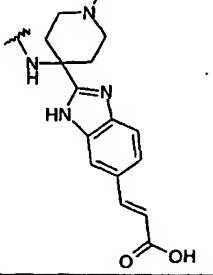
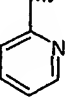

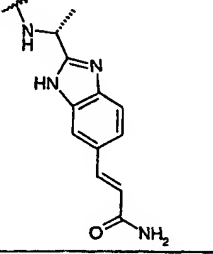
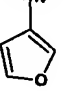
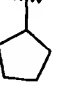
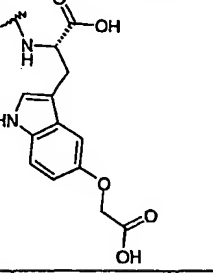
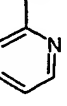

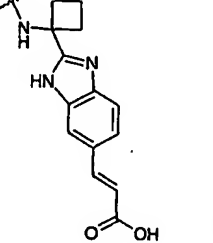
47. A compound of the formula:



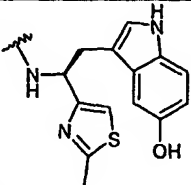


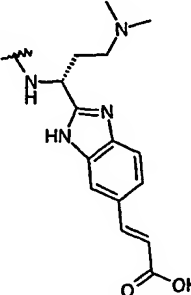


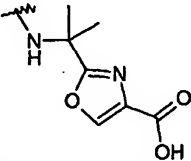


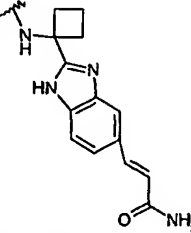


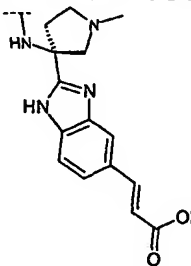


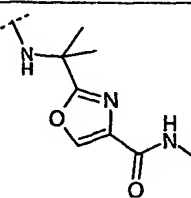
wherein A, R², R³ and Z are defined as follows:

Cpd. #	A	R ²	R ³	Z
1001	NH			
1002	NH			
1003	NH			
1004	NH			
1005	NH			
1006	NMe			

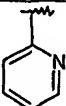
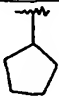
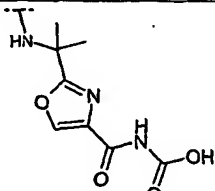
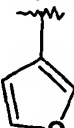
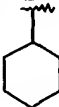
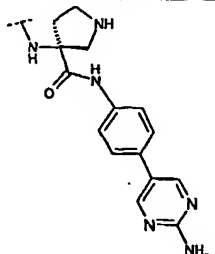
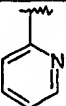
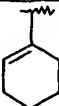
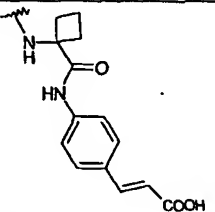
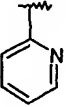
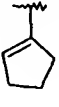
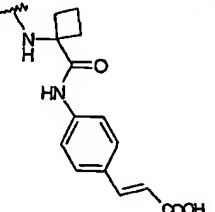
Cpd. #	A	R ²	R ³	Z
1007				
1008	NMe			
1009	NMe			
1010	NMe			
1011	NMe			

Cpd. #	A	R ²	R ³	Z
1012	NMe			
1013	NMe			
1014	NMe			
1015	NMe			
1016	NMe			
1017	NMe			

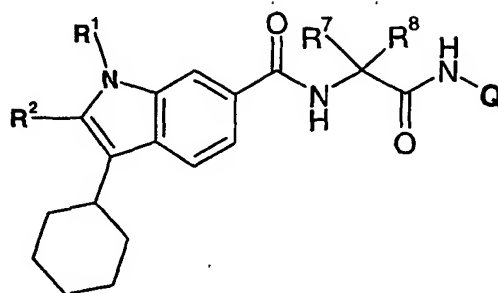
Cpd. #	A	R ²	R ³	Z
1018	NMe			
1019	NH			
1020	NMe			
1021	NMe			
1022	S			
1023	NMe			

Cpd. #	A	R ²	R ³	Z
1024	S			
1025	NMe			
1026	NMe			
1027	NMe			
1028	NMe			
1029	NMe			


282

Cpd. #	A	R ²	R ³	Z
1030	NMe			
1031	NMe			
1032	NMe			
1033	NMe			

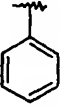
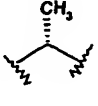
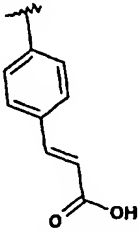
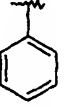

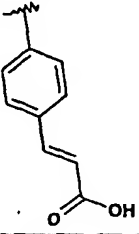

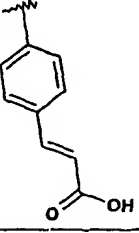
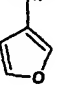
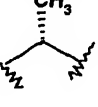
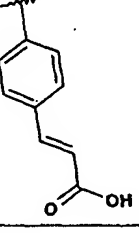
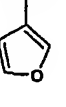

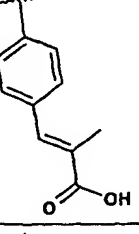


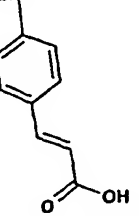
48. A compound of the formula:


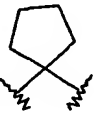
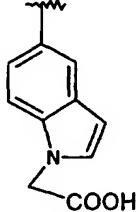

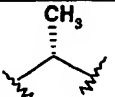
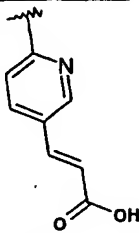

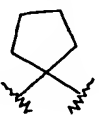
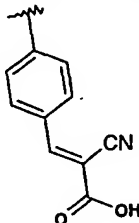

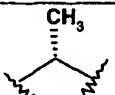
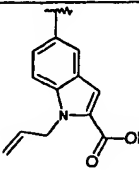

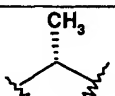
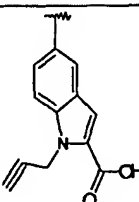


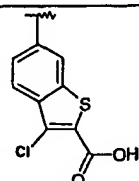


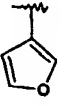
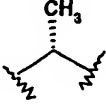
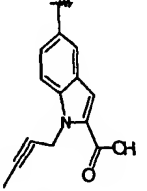
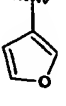
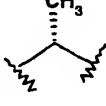
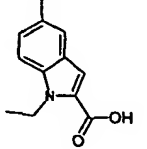
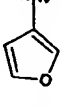
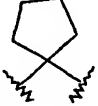
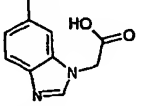
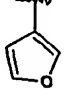

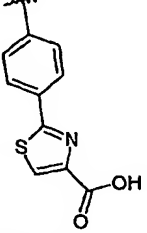
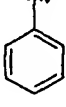

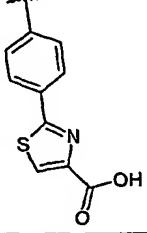
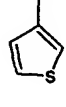

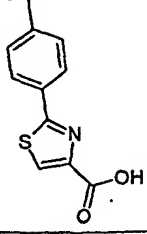
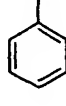

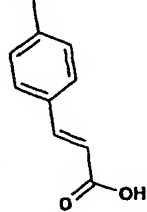
wherein R¹, R², R⁷, R⁸ and Q are defined as follows:

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
				




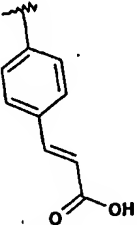



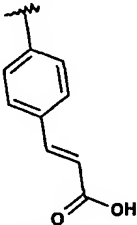

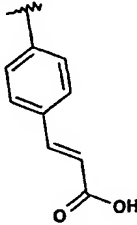


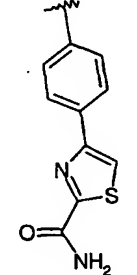

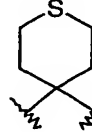
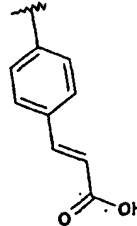
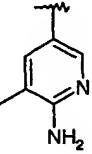

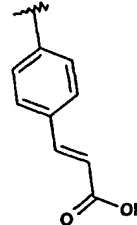
283


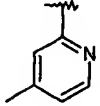

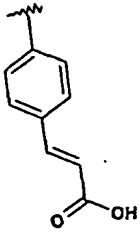
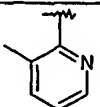

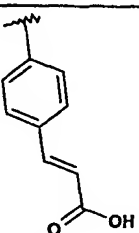
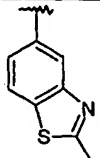

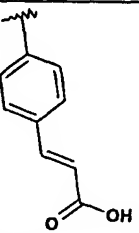
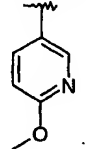

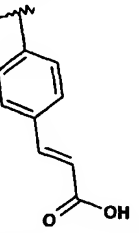
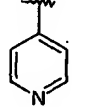

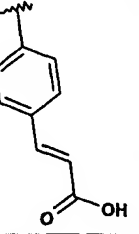
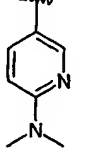

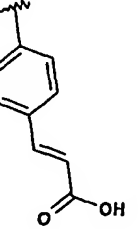
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2001	H			
2002	H			
2003	H	Br		
2004	H			
2005	H			
2006	Me			

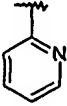

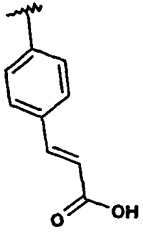
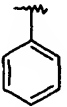

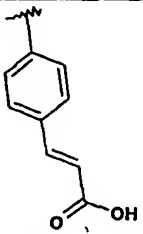
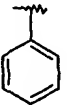

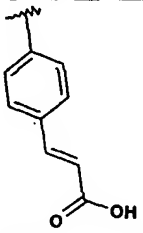
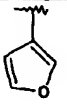

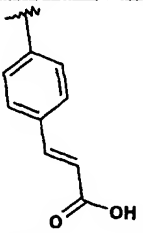
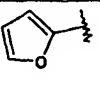

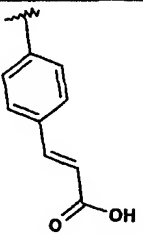
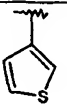

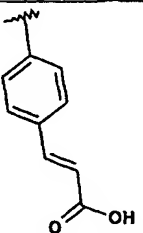
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2008	H			
2009	H			
2010	H			
2011	H			
2012	H			
2013	H			

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2014	H			
2015	H			
2016	H			
2017	H			
2018	H			
2019	H			
2020	Et			



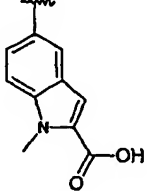
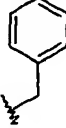


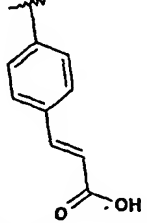


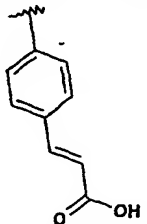


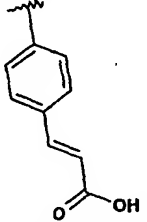



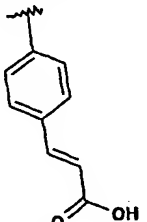


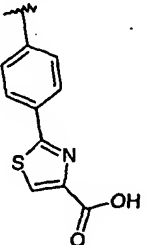
286

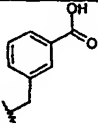
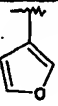
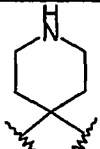
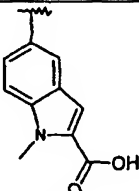
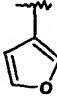

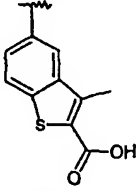
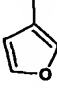
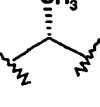
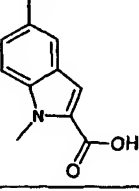
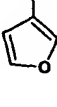

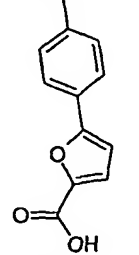
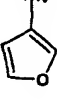
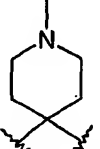
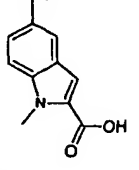


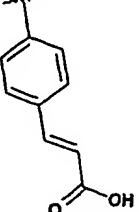
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2021				
2022				
2023	Me	H		
2024	H			
2025	H			
2026	Me			

Cpd. #	R ¹	R ²		Q
2027	Me			
2028	Me			
2029	Me			
2030	Me			
2031	Me			
2032	Me			

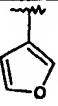

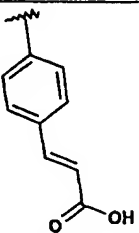
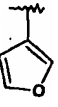
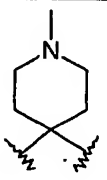
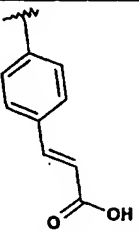
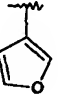

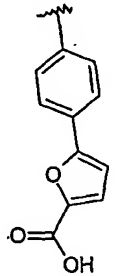
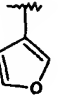

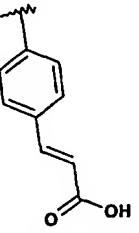
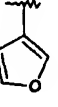
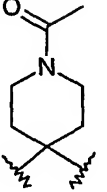
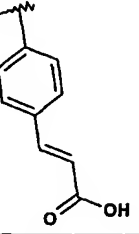
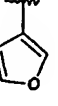
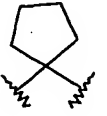
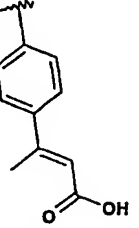
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2033	H			
2034	Me			
2035	H			
2036	H			
2037	H			
2038	H			

289

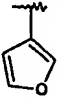

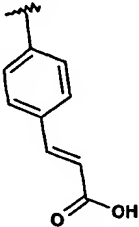


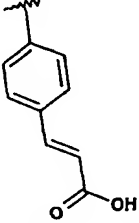


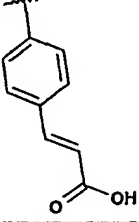


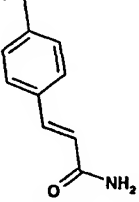


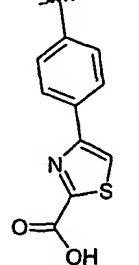


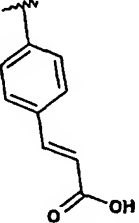
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2039	H			
2040				
2041	Me			
2042	H			
2043				
2044	H			

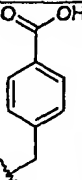
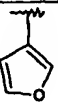

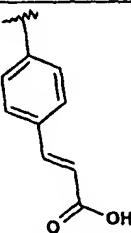
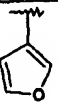
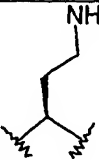
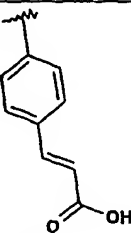
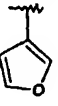
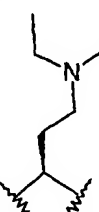
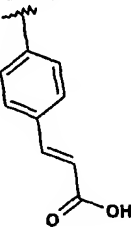


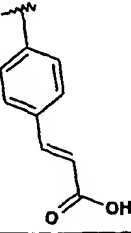
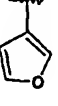
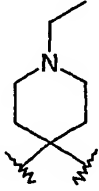
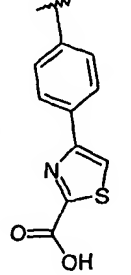
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2045				
2046	H			
2047	H			
2048	H			
2049	H			
2050	H			

291

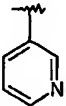

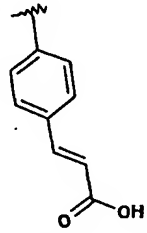

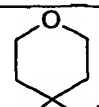
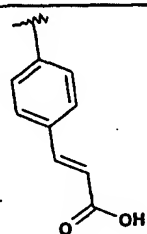
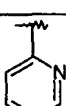
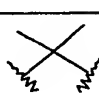
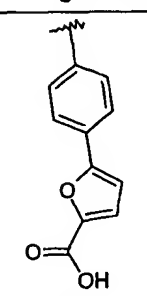
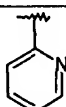

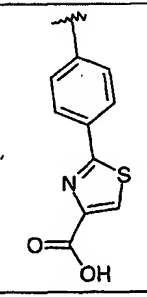
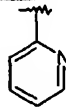

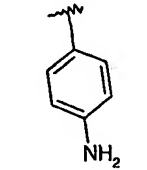
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2051	Me			
2052	H			
2053	H			
2054	Et			
2055	H			
2056	H			

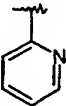

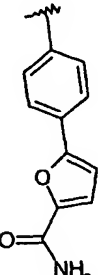
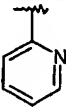

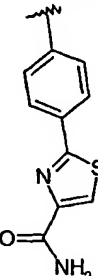
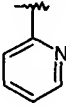

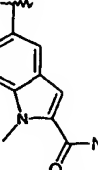
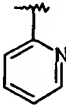

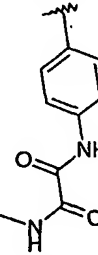
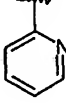

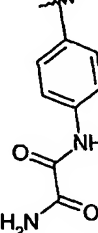
292

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2057	H			
2058	H			
2059	H			
2060	H			
2061	H			
2062	Me			

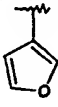
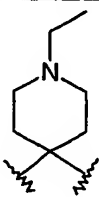
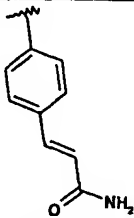
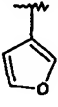
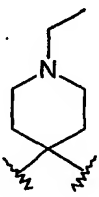
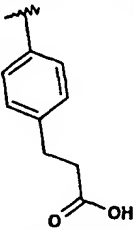
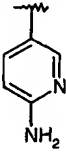

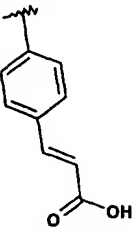
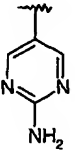

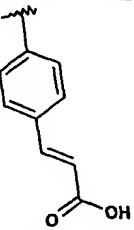
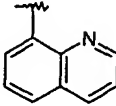

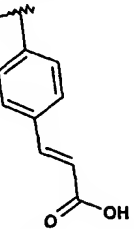
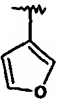
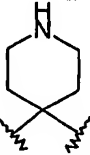
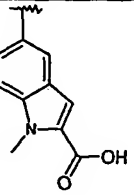
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2063				
2064	H			
2065	H			
2066	Me			
2067	H			

294


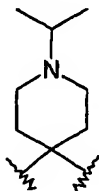
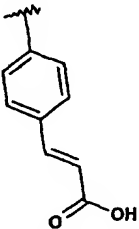
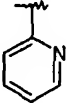

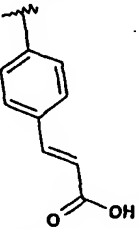

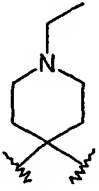
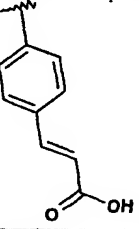
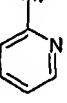

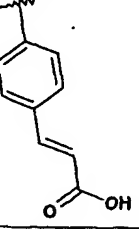
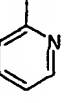

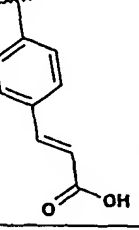
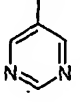

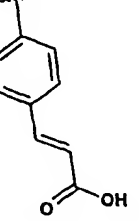
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2068	Me			
2069	H			
2070	Me			
2071	Me			
2072	Me			

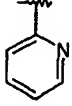
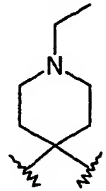
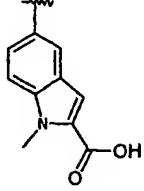
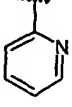

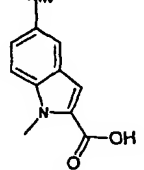
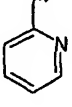

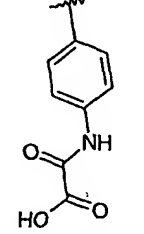
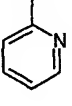

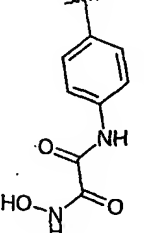
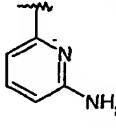

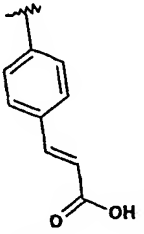
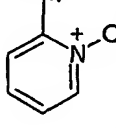

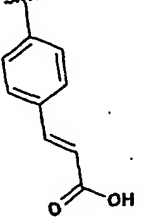
Cpd. #	R ¹	R ²	R⁷ R⁸	Q
2073	Me			
2074	Me			
2075	Me			
2076	Me			
2077	Me			

296


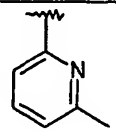

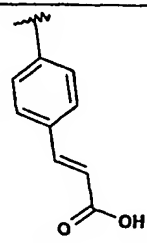
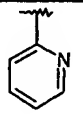
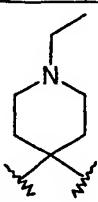
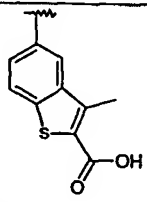
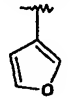
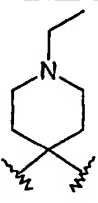
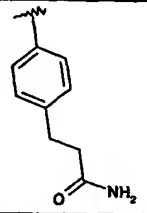
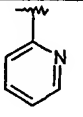
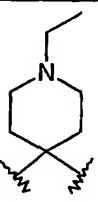
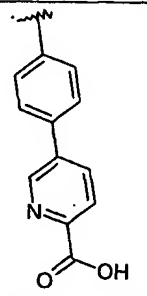
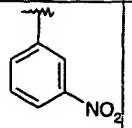

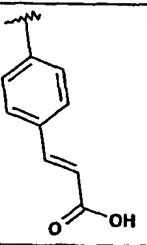
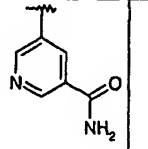

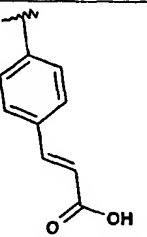
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2078	H			
2079	H			
2080	Me			
2081	Me			
2082	Me			
2084	H			

297

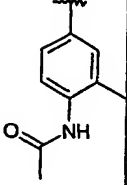

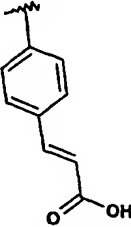
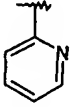
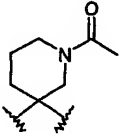
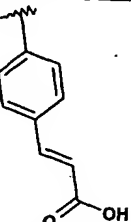
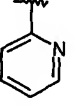
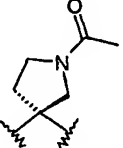
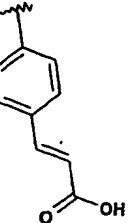
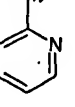

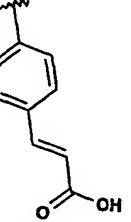
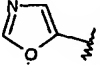

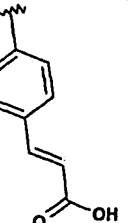
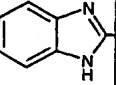

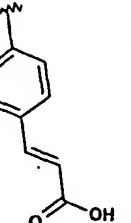
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2086	H			
2087	Me			
2088	H			
2089	H			
2090	Me			
2091	Me			

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2092	Me			
2093	Me			
2094	Me			
2095	Me			
2096	Me			
2097	Me			

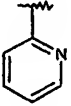
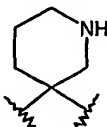
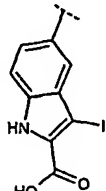
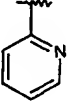

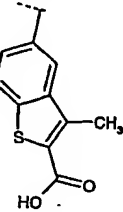
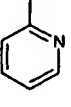

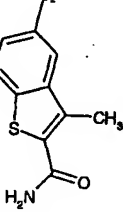
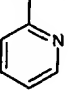

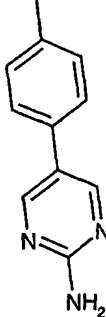
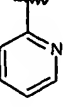
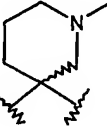
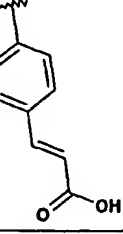
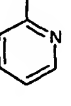

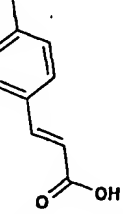
299

Cpd. #	R ¹	R ²		Q
2098	Me			
2099	Me			
2100	H			
2101	Me			
2102	Me			
2103	Me			

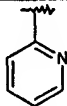

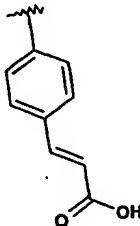
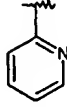

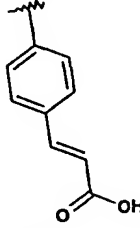
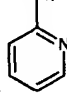

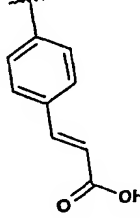
300

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2104	Me			
2105	Me			
2106	Me			
2107	Me			
2108	Me			
2109	Me			

301

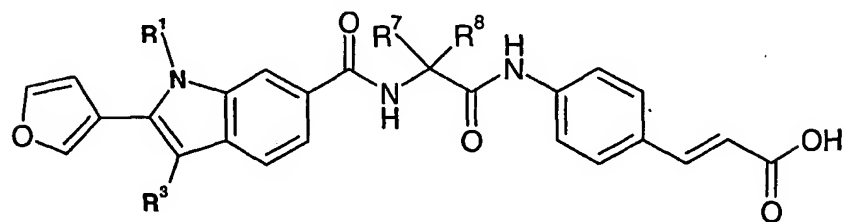
Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2110	Me			
2111	Me			
2112	Me			
2113	Me			
2114	Me			
2115	Me			

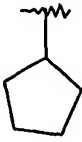

302

Cpd. #	R ¹	R ²	R ⁷ R ⁸	Q
2116	Me			
2117	Me			
2118	Me			

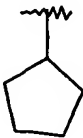

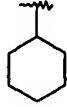
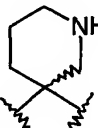
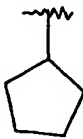

; and

49. A compound of the formula:

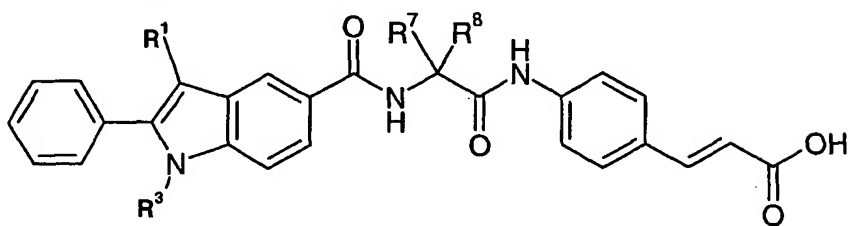
wherein R¹, R³, R⁷ and R⁸ are defined as follows:

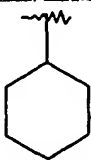



cpd. #	R ¹	R ³	R ⁷ R ⁸
3001	H		

303

3002	H			; and
3003	Me			
3004	Me			

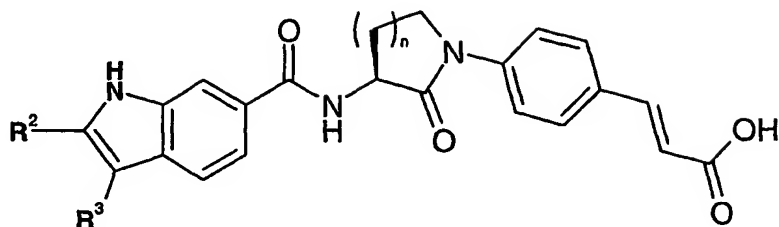
50. A compound of the formula:

wherein R¹, R³, R⁷ and R⁸ are defined as follows:

cpd. #	R ¹	R ³	R ⁷ R ⁸	; and
4001	Me			
4002	H			

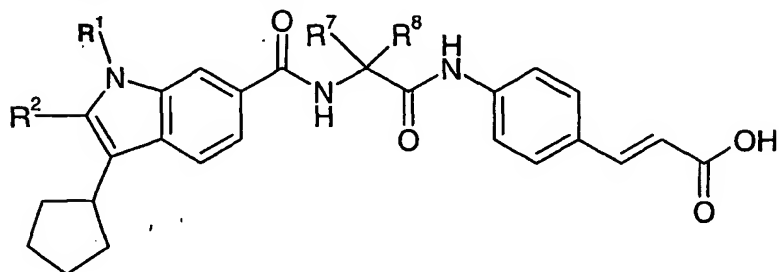
304

51. A compound of the formula:

wherein R^2 , R^3 and n are defined as follows:


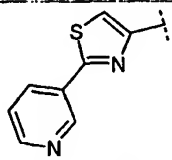
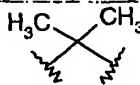
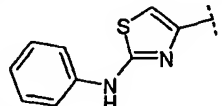
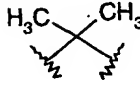
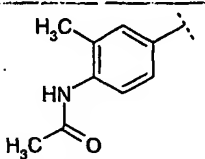

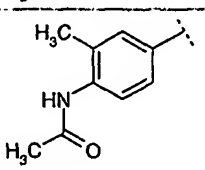

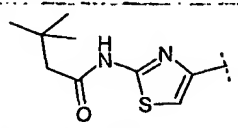

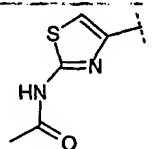

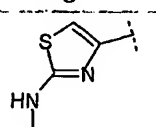
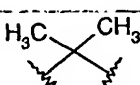
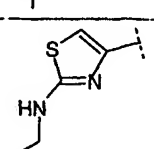
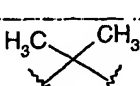
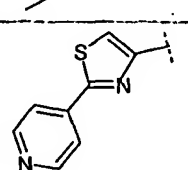
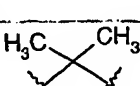
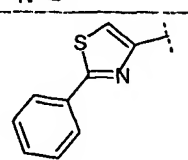

cpd. #	R^2	R^3	n
5001			1

52. A compound of the formula:


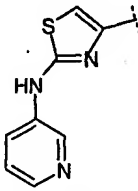
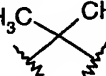
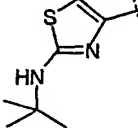

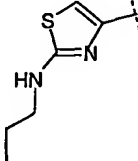
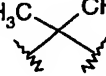
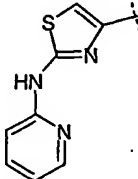
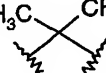
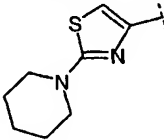
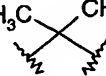
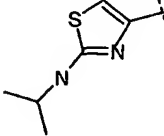
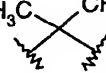
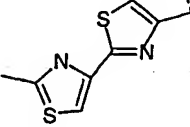

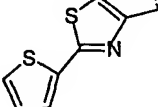

5 wherein R^1 , R^2 , R^7 and R^8 are defined as follows:

cpd. #	R^1	R^2	R^7 R^8
6001	CH ₃		
6002	CH ₃		


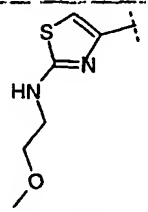
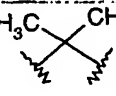
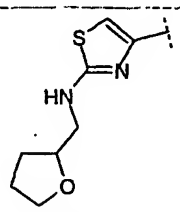

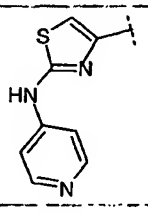
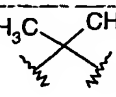
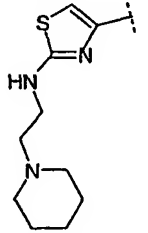
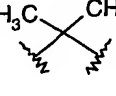
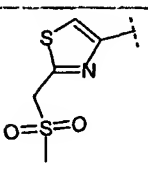
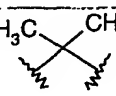
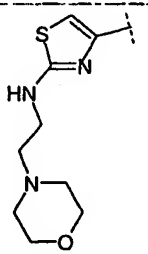
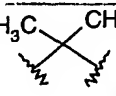
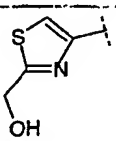
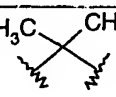
305

cpd. #	R ¹	R ²		
6003	CH ₃			;
6004	CH ₃			;
6005	CH ₃			;
6006	CH ₃			;
6007	CH ₃			;
6008	CH ₃			;
6009	CH ₃			;
6010	CH ₃			;
6011	CH ₃			;
6012	CH ₃			;


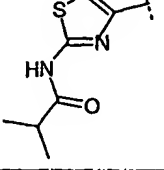

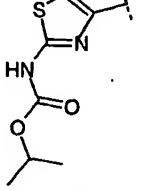

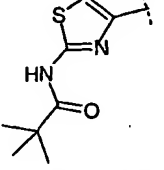

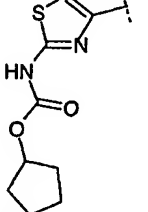

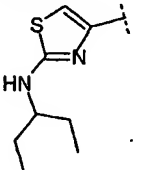
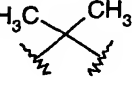
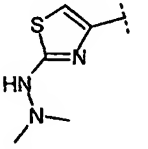
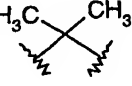
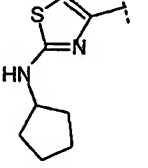

306

cpd. #	R ¹	R ²	
6013	CH ₃		
6013	CH ₃		
6014	CH ₃		
6015	CH ₃		
6016	CH ₃		
6017	CH ₃		
6018	CH ₃		
6019	CH ₃		


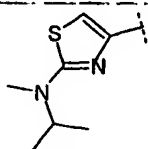
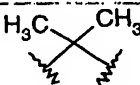
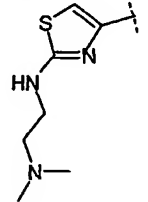
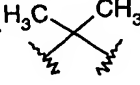
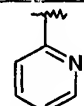

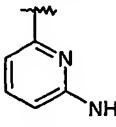

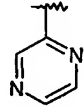

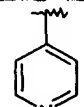

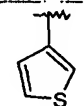

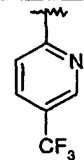

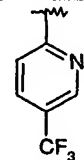

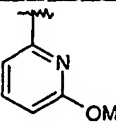

307

cpd. #	R ¹	R ²	
6020	CH ₃		
6021	CH ₃		
6022	CH ₃		
6023	CH ₃		
6024	CH ₃		
6025	CH ₃		
6026	CH ₃		

308

cpd. #	R ¹	R ²		
6027	CH ₃			;
6028	CH ₃			;
6029	CH ₃			;
6030	CH ₃			;
6031	CH ₃			;
6032	CH ₃			;
6033	CH ₃			;

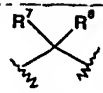
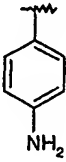
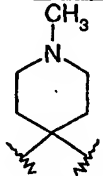
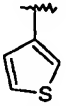

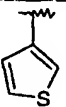
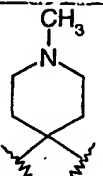
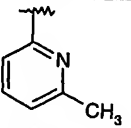

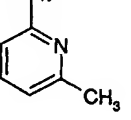
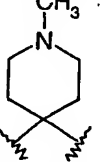
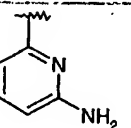
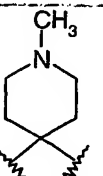
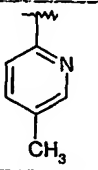

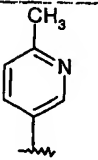

309

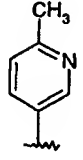
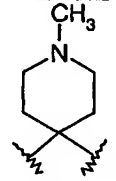
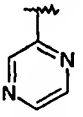

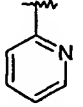

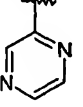
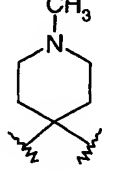
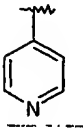
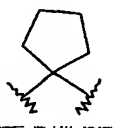
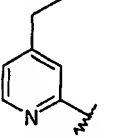
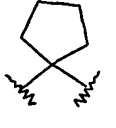
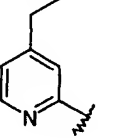
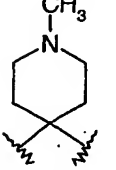
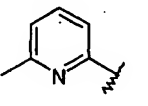
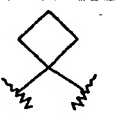
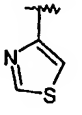
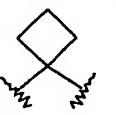
cpd. #	R ¹	R ²		
6034	CH ₃			;
6035	CH ₃			;
6036	CH ₃			;
6037	CH ₃			;
6038	CH ₃			;
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6040	CH ₃			;
6041	CH ₃			;
6042	CH ₃			;
6043	CH ₃			;

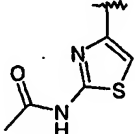

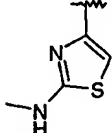

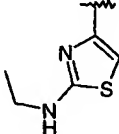

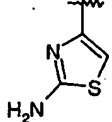

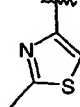

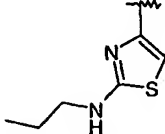
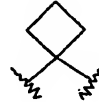
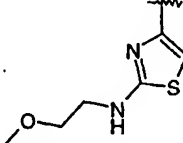

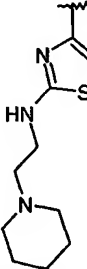

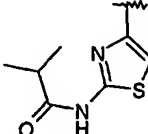
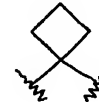
310

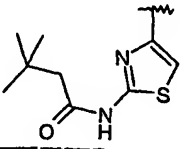
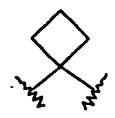
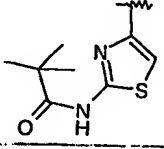
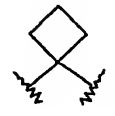
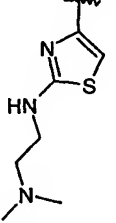
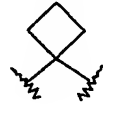
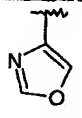



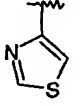

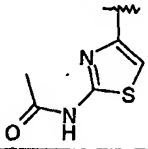

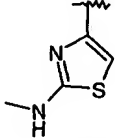
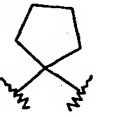
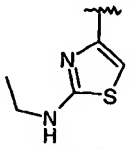
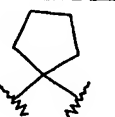
cpd. #	R ¹	R ²	R ⁷ R ⁸
6044	CH ₃		
6045	CH ₃		
6046	CH ₃		
6047	CH ₃		
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6051	CH ₃		
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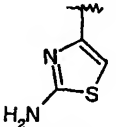
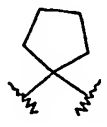
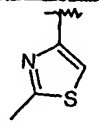
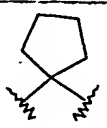
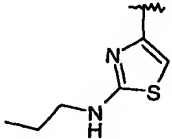
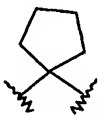
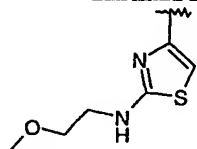

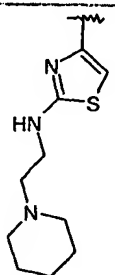

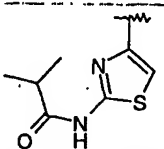

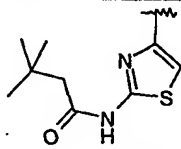

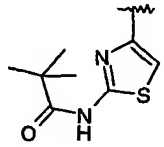

311

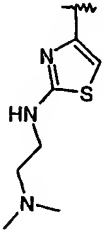

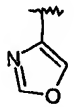


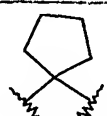
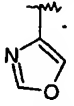

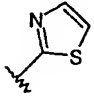
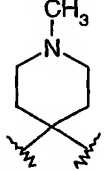
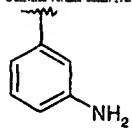
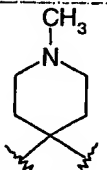
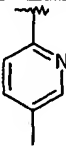
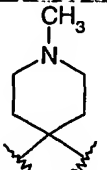
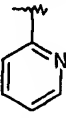
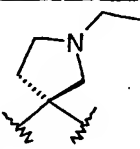

cpd. #	R ¹	R ²		
6054	CH ₃			;
6055	CH ₃			;
6056	CH ₃			;
6057	CH ₃			;
6058	CH ₃			;
6059	CH ₃			;
6060	CH ₃			;
6061	CH ₃			;

cpd. #	R ¹	R ²	R ³ R ⁵	
6062	CH ₃			;
6063	CH ₃			;
6064	CH ₃			;
6065	CH ₃			;
6066	CH ₃			;
6067	CH ₃			;
6068	CH ₃			;
6069	CH ₃			;
6070	CH ₃			;


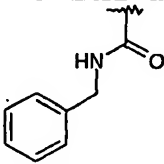

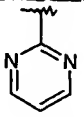

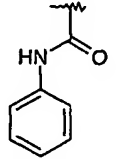


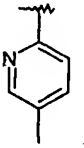

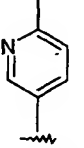

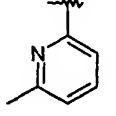

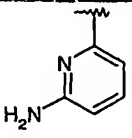

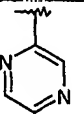

cpd. #	R ¹	R ²	R ⁷ R ⁸
6071	CH ₃		
6072	CH ₃		
6073	CH ₃		
6074	CH ₃		
6075	CH ₃		
6076	CH ₃		
6077	CH ₃		
6078	CH ₃		
6079	CH ₃		

cpd. #	R ¹	R ²	R ⁷ R ⁸
6080	CH ₃		
6081	CH ₃		
6082	CH ₃		
6083	CH ₃		
6084	CH ₃		
6085	CH ₃		
6086	CH ₃		
6087	CH ₃		
6088	CH ₃		

cpd. #	R ¹	R ²	R ¹ R ⁰
6089	CH ₃		
6090	CH ₃		
6091	CH ₃		
6092	CH ₃		
6093	CH ₃		
6094	CH ₃		
6095	CH ₃		
6096	CH ₃		

cpd. #	R ¹	R ²	R ⁷ R ⁶
6097	CH ₃		
6098	CH ₃		
6099	CH ₃		
6100	CH ₃		
6101	CH ₃		
6102	CH ₃		
6103	CH ₃		
6105	CH ₃		
6106	CH ₃	CONHCH ₃	

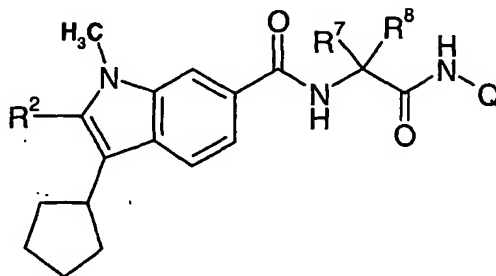
317

cpd. #	R ¹	R ²	R ³ R ⁴
6107	CH ₃	CON(CH ₃) ₂	
6110	CH ₃		
6111	CH ₃		
6112	CH ₃		
6113	CH ₃	CONH ₂	
6114	CH ₃		
6115	CH ₃		
6116	CH ₃		
6117	CH ₃		
6118	CH ₃		

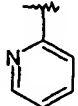

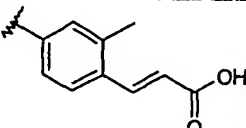
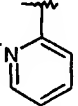
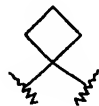
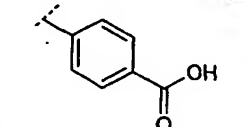
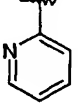

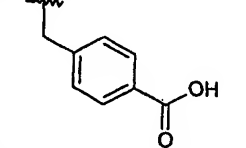
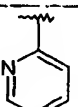

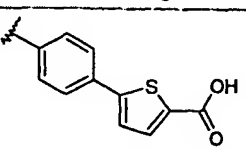
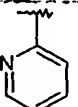

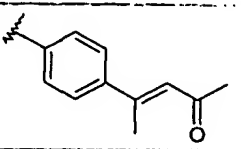
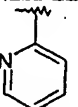

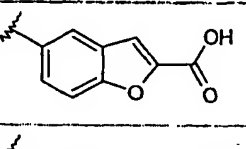
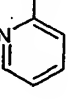

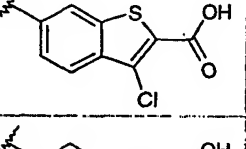
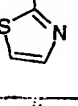

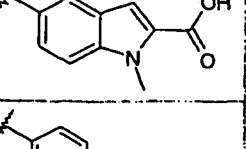


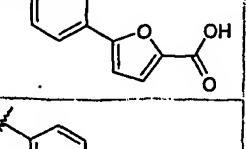


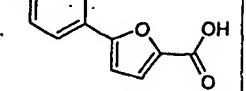
318

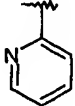
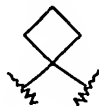
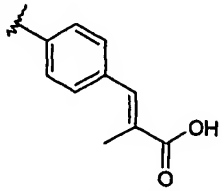
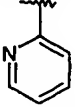

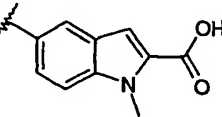
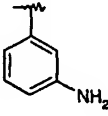

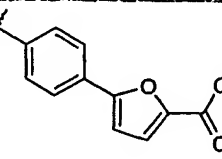
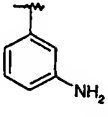

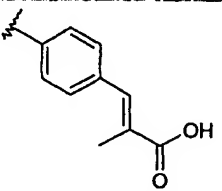
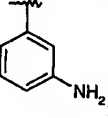

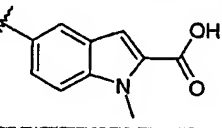
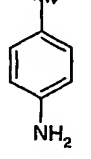

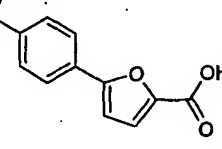
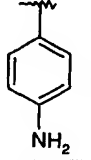

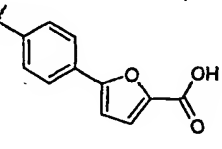
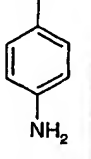

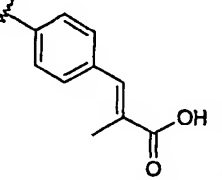
cpd. #	R ¹	R ²	R ⁷ R ⁸	
6119	CH ₃	H		;
6120	CH ₃	Br		;
6121	H			;
6122	CH ₃			;
6123	CH ₃			;
6124	CH ₃			; and
6125	CH ₃			

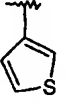

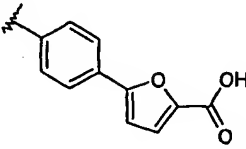
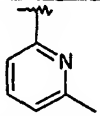

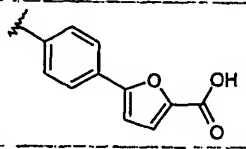
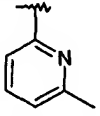

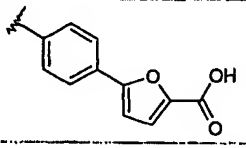
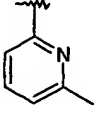

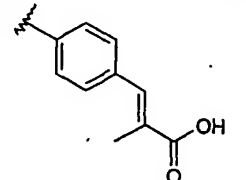
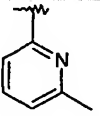
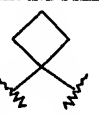
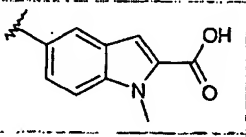
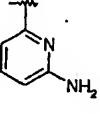

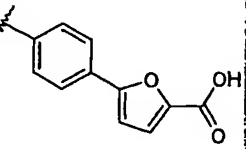
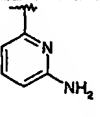

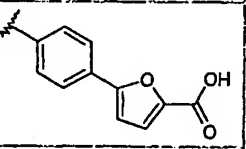
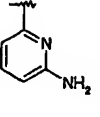

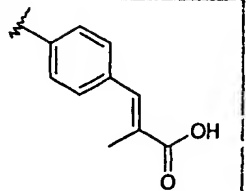
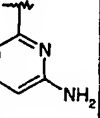
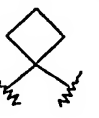
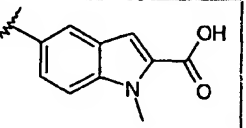
53. A compound of the formula:



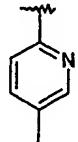
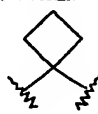
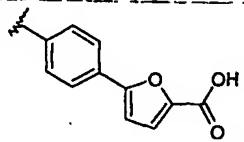
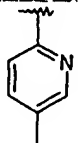

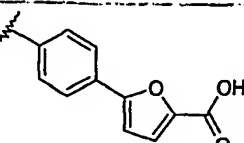
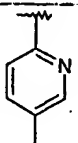

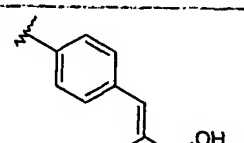
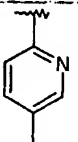

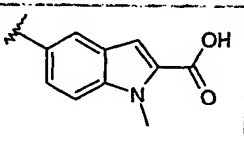
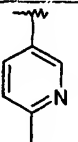

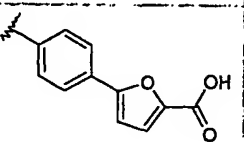
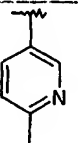

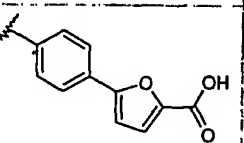
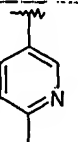

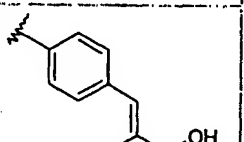
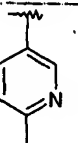
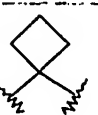
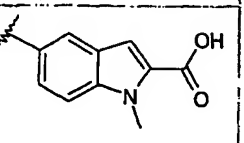
wherein R², R⁷, R⁸ and Q are defined as follows:

cpd #	R ²	R ⁷ R ⁸	Q
7001			
7002			
7003			
7004			
7005			
7006			
7007			
7008			
7009			
7010			

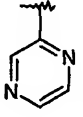

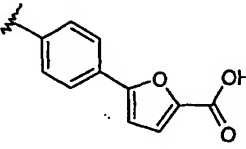
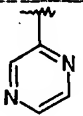

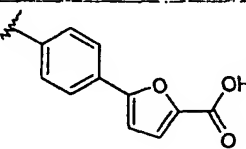
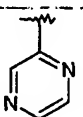

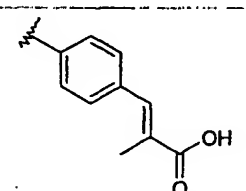
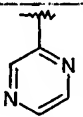

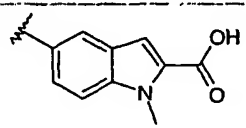
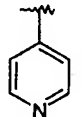

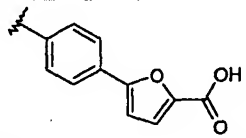
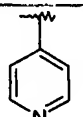

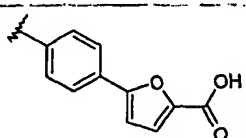
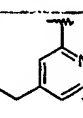

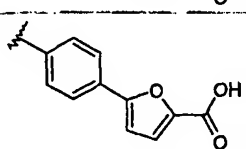
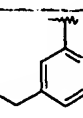

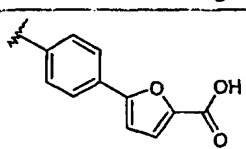
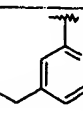

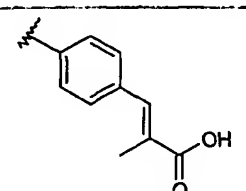
cpd #	R ²	R ⁷ R ⁸	Q
7011			
7012			
7013			
7014			
7015			
7016			
7017			
7018			

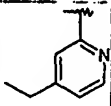

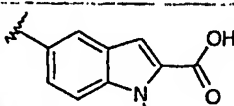
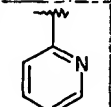

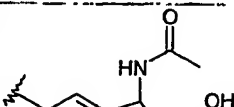
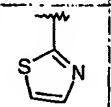

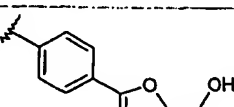
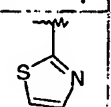

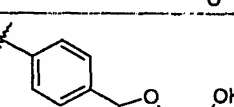
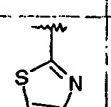

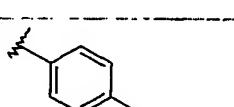
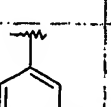

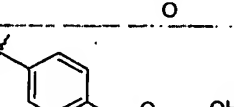
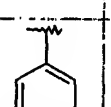

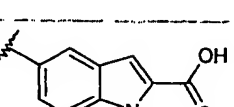
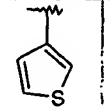

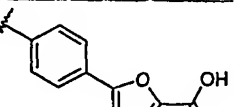
cpd #	R ²	R ⁷ R ⁸	Q
7019			
7020			
7021			
7022			
7023			
7024			
7025			
7026			
7027			

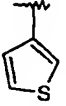

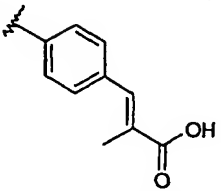
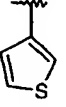

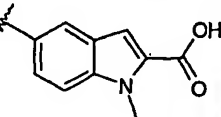
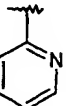

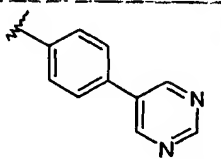
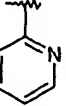

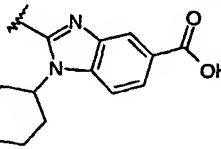
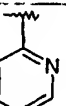
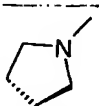
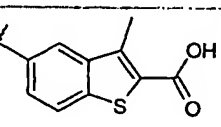
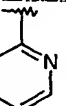
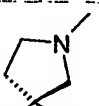
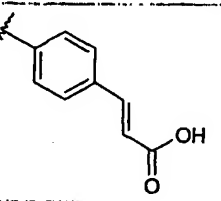
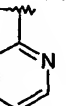
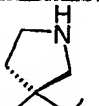
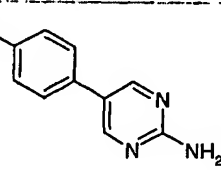
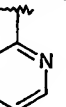
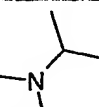
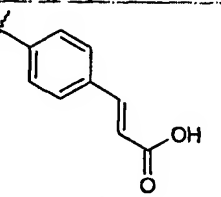
322

cpd #	R ²	R ⁷ R ⁸	Q
7028			
7029			
7030			
7031			
7032			
7033			
7034			
7035			

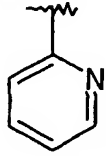

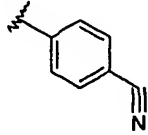
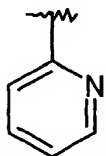

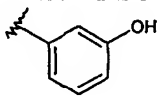
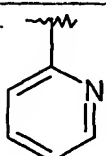

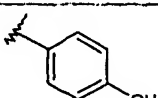
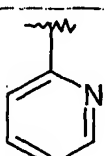

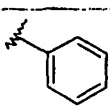
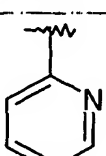

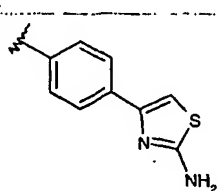
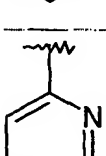
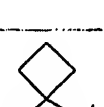
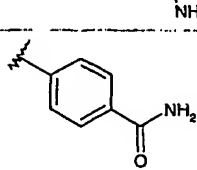
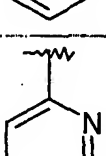
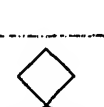
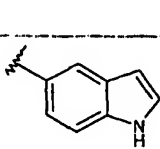
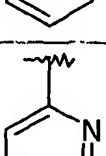
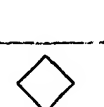
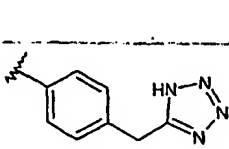
323

cpd #	R ²	R ⁷ R ⁸	Q
7036			
7037			
7038			
7039			
7040			
7041			
7042			
7043			
7044			

cpd #	R ²	R ⁷ R ⁸	Q
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7046			
7047			
7048			
7049			
7050			
7051			
7052			

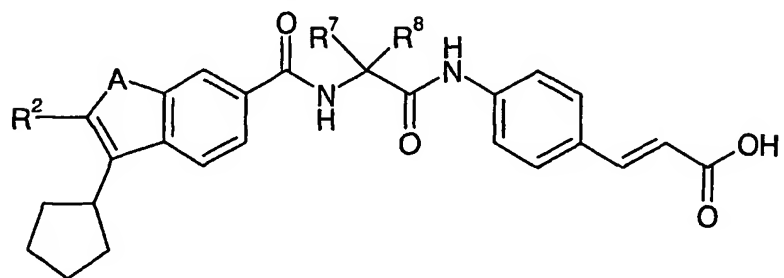
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7054			
7055			
7056			
7057			
7058			
7059			
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cpd #	R ²	$\begin{matrix} R^2 & R^0 \\ \diagup & \diagdown \\ & \end{matrix}$	Q
7061			
7062			
7063			
7064			
7065			
7066			
7067			
7068			
7069			

cpd #	R ²	R ⁷ R ⁸	Q
7070			
7071			
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7083			

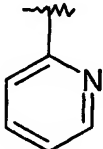
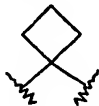
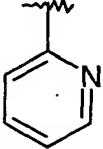

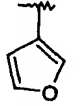

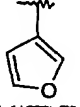

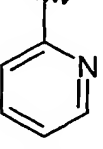

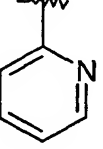

54. A compound of the formula:



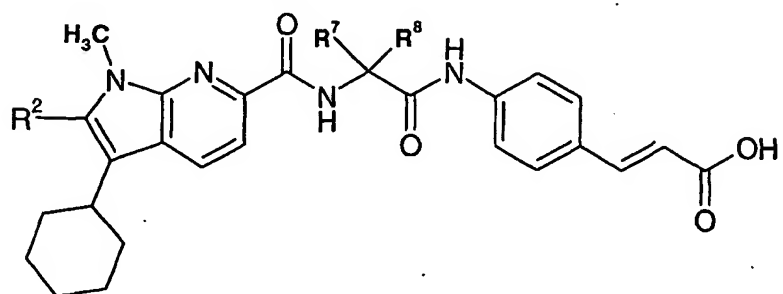
wherein A, R², R⁷ and R⁸ are defined as follows:

cpd. #	A	R ²	R ⁷ R ⁸


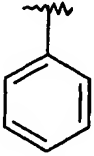

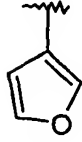

329

cpd. #	A	R ²	R ⁷ R ⁸	
8001	S			;
8002	S			;
8003	S			;
8004	S			;
8005	O			; and
8006	O			

55. A compound of the formula:



wherein R², R⁷ and R⁸ are defined as follows:

cpd. #	R ²	
9001		
9002		

; and

56. A compound of the formula I according to claim 1, or a pharmaceutically acceptable salt thereof, as an inhibitor of RNA dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV.

57. A compound of the formula I according to claim 1, or a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

58. A pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

59. A composition according to claim 58, further comprising an immunomodulatory agent.

5

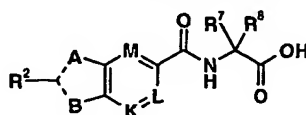
60. A composition according to claim 59, wherein said immunomodulatory agents is selected from: α -, β -, δ - γ -, and ω -interferon.

61. A composition according to claim 58, further comprising another antiviral agent.

62. A composition according to claim 61, wherein said antiviral agent is selected from: ribavirin and amantadine.

331

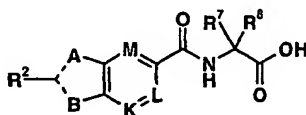
63. A composition according to claim 58, further comprising another inhibitor of HCV polymerase.
64. A composition according to claim 58, further comprising an inhibitor of: HCV helicase, HCV protease, HCV metalloprotease or HCV IRES.
65. Use of a compound of formula I according to claim 1, for the manufacture of a medicament for the treatment of HCV infection.
66. An intermediate compound represented by formula 1c:



1c

- 5 wherein A, R², B, K, L, M, R⁷ and R⁸ are as defined in claim 1, or a salt, or a derivative thereof.

67. A process for producing compounds of formula I, comprising:
a) coupling, in a mixture containing an aprotic solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1c:

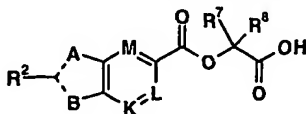


1c

10

- with amine Q-NH₂ so as to produce compounds of formula I, wherein A, R², B, R⁷, R⁸, Q, K, L, M and Q are as defined in claim 1.

68. An intermediate compound represented by formula 1d:

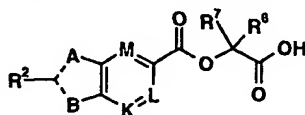


1d

- 15 wherein A, R², B, K, L, M, R⁷ and R⁸ are as defined in claim 1, or a salt or a derivative thereof.

69. A process for producing compounds of formula I, comprising:

a) coupling, in a mixture containing an appropriate solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1d:



1d

- 5 with amine Q-NH₂ so as to produce compounds of formula I, wherein A, R², B, R⁷, R⁸, Q, K, L, and M are as defined in claim 1.

SEQUENCE LISTING

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26

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International Bureau(43) International Publication Date
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401/14, 409/14, 413/14, 405/04, 401/04, 417/04, 409/04,
413/04(CA). GILLARD, James [CA/CA]; 2100 Cunard Street,
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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
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(CA).(84) Designated States (*regional*): ARIPO patent (GH, GM,
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Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
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TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

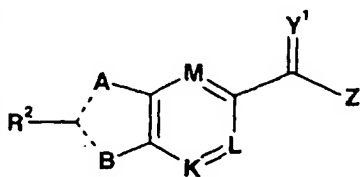
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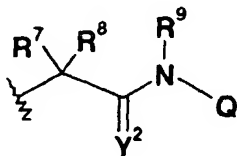
— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments(88) Date of publication of the international search report:
30 May 2003

[Continued on next page]

(54) Title: HEPATITIS C VIRUS POLYMERASE INHIBITORS WITH A HETEROBICYCLIC STRUCTURE



(I)



(II)

(57) Abstract: An isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I: wherein: A is O, S, NR¹, or CR¹, wherein R¹ is defined herein; represents either a single or a double bond; R² is selected from: H, halogen, R²¹, OR²¹, SR²¹, COOR²¹, SO₂N(R²²)₂, N(R²²)₂, CON(R²²)₂, NR²²C(O)R²² or NR²²C(O)NR²² wherein R²¹ and each R²² is defined herein; B is NR³ or CR³, with the proviso that one of A or B is either CR¹ or CR³, wherein R³ is defined herein; K is N or CR⁴, wherein R⁴ is defined herein; L is N or CR⁵, wherein R⁵ has the same definition as R⁴; M is N or CR⁷, wherein R⁷ has the same definition as R⁴; Y¹ is O or S; Z is N(R^{6a})R⁶ or OR⁶, wherein R^{6a} is H or alkyl or NR⁶¹R⁶² wherein R⁶¹ and R⁶² are defined herein; and R⁶ is H, alkyl, cycloalkyl, alkenyl, Het, alkyl-aryl, alkyl-Het; or R⁶ is wherein R⁷ and R⁸ and Q are as defined herein; Y² is O or S; R⁹ is H, (C₁₋₆ alkyl), (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl, aryl, Het, (C₁₋₆)alkyl-aryl or (C₁₋₆)alkyl-Het, all of which optionally substituted with R⁹⁰; or R⁹ is covalently bonded to either of R⁷ or R⁸ to form a 5- or 6-membered heterocycle; a salt or a derivative thereof, as an inhibitor of HCV NS5B polymerase.



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/CA 02/01128

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/404 A61K31/381 C07D417/14 C07D403/12 C07D209/08
 C07D405/12 C07D405/14 C07D401/14 C07D409/14 C07D413/14
 C07D405/04 C07D401/04 C07D417/04 C07D409/04 C07D413/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 47883 A (JAPAN TOBACCO INC (JP)) 5 July 2001 (2001-07-05) cited in the application abstract page 1 examples 32-34, 37, 53, 281, 503 claims & EP 1 162 196 A1 ---	1-69
X	US 5 059 621 A (C.I.R.D. (FR)) 22 October 1991 (1991-10-22) formulae (I)-(IV), columns 1-3 claims; examples ---	1-55, 66-69
X	US 6 069 156 A (FUJISAWA PHARMACEUTICAL CO LTD (JP)) 30 May 2000 (2000-05-30) formula I, column 1 claims; examples ---	1-55, 66-69
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Further documents are listed in the continuation of box C.



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 & document member of the same patent family

Date of the actual completion of the International search

4 April 2003

Date of mailing of the International search report

11/04/2003

Name and mailing address of the ISA

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Authorized officer

Cortés, J

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 02/01128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/04 C07D471/04

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 48697 A (RHONE-POULENC RORER LTD (GB)) 24 December 1997 (1997-12-24) claims; examples ---	1-55, 66-69
X	JP 10 067682 A (FUJISAWA PHARMACEUT CO LTD (JP)) 10 March 1998 (1998-03-10) claims; examples ---	1-55, 66-69
X	JP 10 114654 A (FUJISAWA PHARMACEUT CO LTD (JP)) 6 May 1998 (1998-05-06) claims; examples ---	1-55, 66-69
X	JP 09 124632 A (SANKYO CO LTD (JP)) 13 May 1997 (1997-05-13) claims; examples --- -/--	1-55, 66-69

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 April 2003

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

Cortés, J

INTERNATIONAL SEARCH REPORT

 Inter national Application No
 PCT/CA 02/01128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 32653 A (CEPHALON INC (US)) 10 May 2001 (2001-05-10) page 1, line 21 e.g. compounds no. 16, 50, 115, 116, 211, 237-239, 251, 255, 258, ---	1-55, 66-69
X	US 3 565 912 A (UPJOHN CO (US)) 23 February 1971 (1971-02-23) formula IX, examples ---	1-55, 66-69
X	JP 2001 122855 A (JAPAN TOBACCO INC (JP)) 8 May 2001 (2001-05-08) formula (1) e.g. compounds 1-29 to 1-31 ---	1-55, 66-69
X	WO 01 30774 A (AVENTIS PHARMA DEUTSCHLAND GMBH (DE)) 3 May 2001 (2001-05-03) claims; examples ---	1-55, 66-69
X	US 5 912 260 A (JAMES BLACK FOUNDATION LTD. (UK)) 15 June 1999 (1999-06-15) formula (I), examples ---	1-55, 66-69
X	US 4 740 519 A (CENTRE NATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D. (FR)) 26 April 1988 (1988-04-26) formula (I), examples ---	1-55, 66-69
X	EP 0 987 250 A (SHIONOGI & CO LTD (JP)) 22 March 2000 (2000-03-22) e.g. intermediates of formulae (VII) and (VIII) ---	1-55, 66-69
X	WO 99 28297 A (BOEHRINGER INGELHEIM PHARMA (DE)) 10 June 1999 (1999-06-10) claims; examples ---	1-55, 66-69
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X	WO 01 47922 A (AVENTIS PHARMA LTD (GB)) 5 July 2001 (2001-07-05) claims; examples ---	1-55, 66-69
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-46 (part), 56-69 (part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds with the structural features of the compounds in claims 47-55, i.e. compounds of formula (I) according to claim 1, wherein:

1) A is O, S or NR₁; B is CR₃; K is CR₄; L is CR₅; Y₁ is O; R₂ is cycloalkyl, aryl or heterocyclyl; R₃ is C₃-C₇ cycloalkyl; and the remaining substituents as defined in claim 1.

2) A is CR₁; B is NR₃; M is CR₇; K is CR₄; L is CR₅; Y₁ is O; R₂ is cycloalkyl, aryl or heterocyclyl; R₃ is C₃-C₇ cycloalkyl; and the remaining substituents as defined in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-46 (part), 56-69 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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